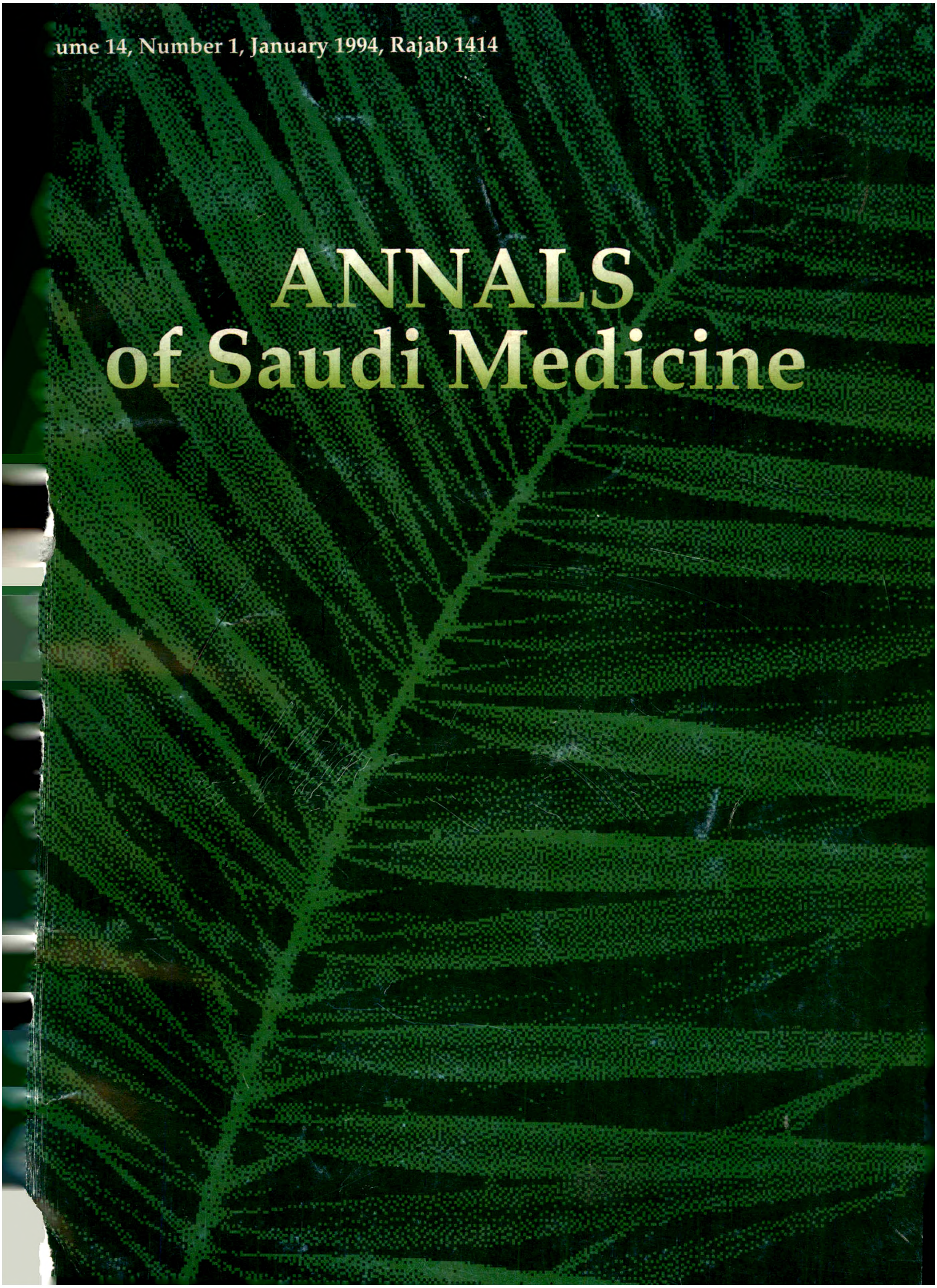

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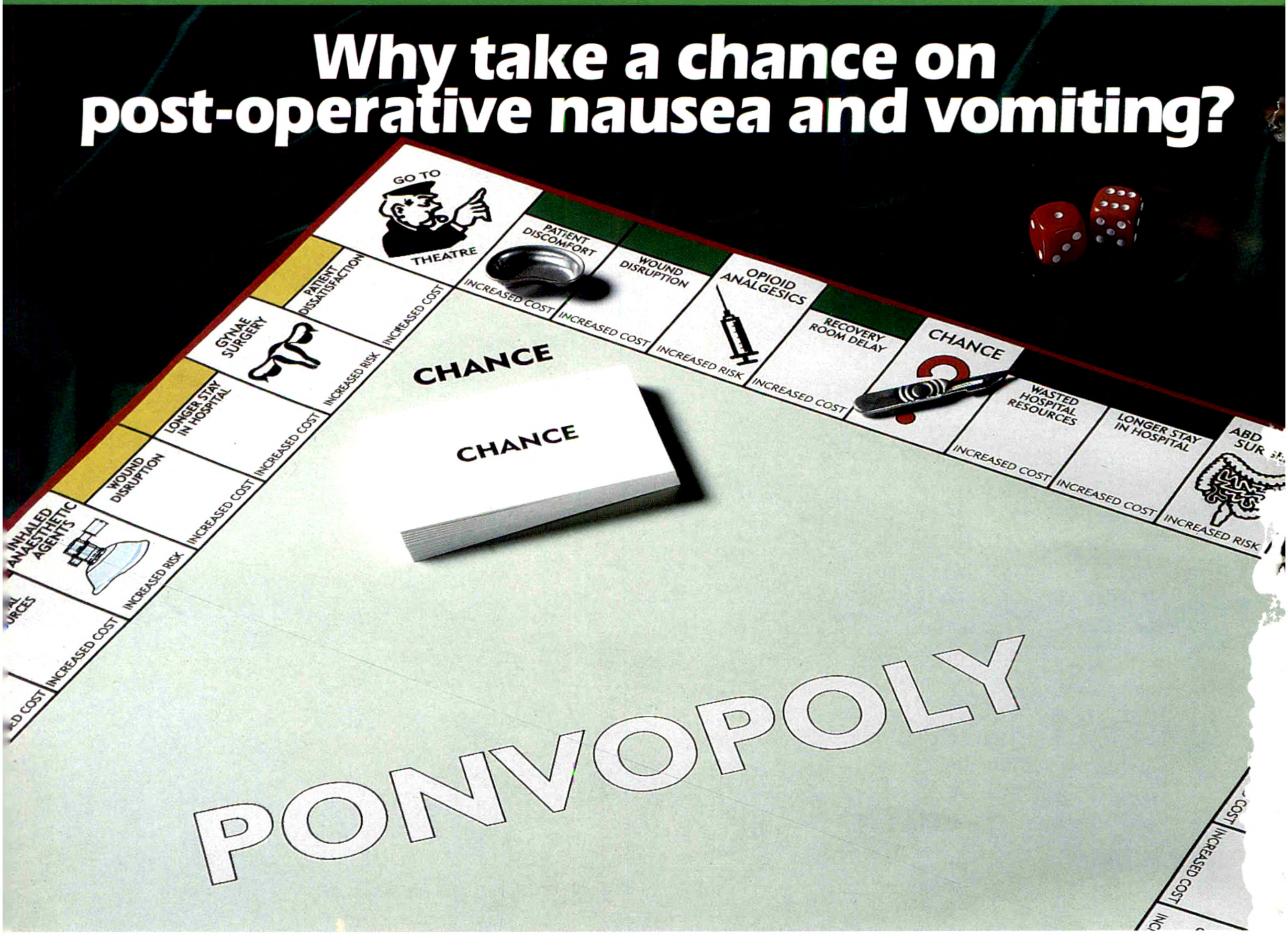

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Editorial

COMMERCIAL RENAL TRANSPLANTATION: CLINICAL AND ETHICAL ISSUES

It is truly devastating for patients to learn that they have end stage renal disease (ESRD). This is because this entity perpetrates immense physical, financial and psychological suffering and requires lifelong commitment to medical care. Furthermore, in the absence of renal replacement therapy, it equals certain death.

In the early 1960s, dialysis became available in Western countries. Within three decades, treatment of patients with ESRD has evolved from a desperate attempt to save life to a large, costly, but routinely available clinical service that sustains hundreds of thousands of lives throughout the world. Consequent to this, the number of patients accepted into dialysis programs continues to increase. Unfortunately, dialysis in most developing countries is not so widely available, and in some, does not even exist. However, in Saudi Arabia and other affluent Gulf States, both government and private sectors have made dialysis available to all patients with ESRD. Despite this, dialysis facilities in these countries are now significantly overcrowded with patients.

The only definitive solution to the problem of ESRD is kidney transplantation because it is less expensive and offers a better quality of life than maintenance dialysis. Before 1965G, both related and nonrelated donors were accepted for renal transplantation in the United States; nonrelated living donors provided approximately 10% of all transplanted kidneys. However, most of the donors were either spouses or friends, who had a vested interest in the well-being of the recipient and, therefore, the motives were purely altruistic. In 1965G, data from the registry in Human Kidney Transplantation from these donors showed poor results. Because of this and the increasing availability of dialysis, concern over the risk to the donor, and the question of the donor's motivation, the living nonrelated donors were deemed unacceptable.[1] On the other hand, conventional sources of kidneys from living related and cadaveric donors proved to be insufficient in meeting the increasing demand. In almost all countries, the number of kidney transplants performed annually still lag behind the number of new patients with ESRD accepted into dialysis programs. In Saudi Arabia, approximately 325 new patients develop ESRD each year. The total number of transplants performed within the Kingdom and outside does not exceed 150 to 200 per year. Therefore, and as can be expected, the number of dialysis patients will continue to increase.

The lack of adequate dialysis facilities and the shortage of kidneys, particularly in India, have induced some institutions to start transplantation from living nonrelated donors for monetary compensation. Subsequently, advertisements began to appear in the national press from patients in need of kidneys as well as from people willing to donate their kidneys for financial reward. In this environment, wicked entrepreneurs seized the opportunity and began to trade human kidneys where the poor were induced by payment to donate their kidneys. It was then discovered by patients from other countries, including the Gulf States, that they were able to receive kidney transplantation from nonrelated donors in India. During the early 1980s, some patients traveled to India, most often without the knowledge of their physicians, and then returned to us for follow-up after receiving a living nonrelated renal transplantation in India. After 1985G, the pace of this type of transplantation began to accelerate until it became the preferred modality of transplantation among patients who developed ESRD. Many patients had more than one related potential donor but preferred to go for living nonrelated renal transplantation in order to avoid "harm" to one of their healthy relatives. Other patients desperately looked for a "quick fix", sometimes even in the presence of a clear contraindication for transplantation. Similarly, a number of poor Turkish donors were lured into selling their kidneys in Germany and England. Initially, the donors sell their kidneys in order to support their families with the monies received. Presently, the motives are different and vary from buying new luxury items, such as televisions or video recorders, to starting new businesses.

This practice of living nonrelated renal transplantation is simply a commercial transaction where profit, not patient care, is the primary motive. Consequently, the standard of medical practice is likely to be compromised. This unconventional source of kidneys has generated intense criticism and worldwide condemnation. Moreover, a flurry of resolutions against this practice began to appear. In 1987G, a Unified Arab Draft Law on Human Organ Transplants was adopted by the Council of Arab Ministers of Health. Article 7 of the text states that the sale, purchase or remunerated donation of human organs is prohibited and that no specialist, knowing an organ to have been acquired by such means, may use it in a transplant operation.[2] In Islam, opposition to trade in human organs was expressed by the Council of Ulama which stated that selling one's organs is strictly forbidden. Trade in human organs was also condemned by several other regional and international organizations such as the World Health Organization (WHO), The Transplantation Society, The World Medical Association, The Council of Europe, and The British Transplantation Society.[3] The complex issues involved were also discussed in several International Congresses of the Transplantation Society in Sydney, Australia in 1988G, International Congress on "Ethics, Justice, and Commerce in Transplantation" in Ottawa, Ontario, Canada in 1989G, in the European Dialysis and Transplant Association/European Renal Association (EDTA/ERA) in Munich, Germany in 1990G and in Chicago, IL, USA in 1992G. In these Congresses, many physicians, lawyers, ethicists, and philosophers from various countries as well as physicians involved in the practice in India addressed the Congresses.[4] Those opposing commercial transplantation argued that: 1) the practice is abhorrent to the conscience of civilized societies; 2) patient care is relegated to the laws of the marketplace; 3) unscrupulous brokers, and their methods, are reminiscent of the slave trade; 4) the welfare of donors and their families are not safeguarded; 5) transplant results are inferior; and 6) this practice may hinder efforts to establish and promote cadaver and live related donor transplantation programs. However, the solutions they propose to the worldwide shortage of transplantable organs have not been largely successful. By contrast, physicians involved in this type of transplantation maintained that: 1) a significant number of related donors, at least in India, receive monetary or material compensation; 2) the financial gain contributes to the welfare of the entire family, and the harm to the nonrelated donor from the surgical procedure is minimal. In fact, the donors may be offered a substantial net medical gain; 3) the majority of patients who have undergone living nonrelated renal transplantation have come from middle and salaried classes; 4) results of living nonrelated renal transplantation are comparable to those of other types of transplantation; 5) there is no evidence to prove that this practice acted as a disincentive to live related and cadaver transplants; and 6) legislation prohibiting living nonrelated renal trans-plantation would only drive the business underground to the ultimate detriment of both the donor and the patient.[5]

In addressing this problem, one must not have tunnel vision where the focus is mainly on condemning the sale of human organs. If we look at the issue from the patient's point of view, we may begin to understand why or how commercial transplantation came into existence. When a patient first learns that he has kidney failure, he immediately realizes that his life will never be the same again. He is also told that he should be on maintenance dialysis, has to restrict his diet and fluid intake, has to take medication for the rest of his life, and that he needs to make the necessary arrangements for dialysis before he can travel. Not only that, but he also finds out quickly that dialysis facilities are overcrowded and private dialysis is quite expensive. This situation can only be described as being very frustrating. Therefore, it is rational for him and his family to search for a definitive answer to this intricate problem. For him, renal transplantation needs to be done, and the sooner, the better. Then he is told that there are not enough cadaver kidneys for transplantation if he does not have a willing related donor. Then someone indicates that he can obtain a kidney from India within two to four weeks. The patient finds this an easy way out and therefore goes for it, even if it means going against medical advice.

While it was reported that the results of this type of transplantation are inferior to other types of transplantation, the issue is far from being settled.[6,7] Results of nonrelated but emotionally related donor transplants in our institution as well as in the United States are comparable to cadaver transplants.[8,9] Most studies pertaining to commercial transplantation were from tertiary care centers where many patients were referred because of a complicated post transplant course, and therefore results may not be representative of the true results achieved in this type of transplantation. We are currently analyzing the results of a large multicenter study in which 540 patients with living nonrelated renal transplantations performed in India were included. In the first phase of the study, we evaluated the attitudes of physicians toward this type of transplantation.[10] The results of our survey clearly show that patients with ESRD take the initiative in seeking living nonrelated renal transplantations despite physician discouragement and significant financial burden. The transplants were performed expeditiously and patients returned to their home countries within a short period of time with poor or no medical reports. Responding centers felt that patient education was inadequate and their compliance with medications and follow-up visits were poor or only fair. Seventy-five percent of centers thought that the medical report that was sent with patients was poor or only fair. More than half of the centers thought that living nonrelated renal transplantation was associated with high mortality. All centers recommended that more should be done to improve public education about this type of transplantation. The results also demonstrated that the majority of physicians from the participating centers were solidly opposed to this practice and wanted it to be discontinued.

I am convinced, like many of my colleagues, that commercial transplantation has a significant negative influence on our efforts to establish and nourish local cadaveric renal transplant programs. We observed a negative relationship between the number of patients who had living nonrelated renal transplantation performed in India who returned for routine post transplant follow-up and patients who had living related renal transplants performed at King Faisal Specialist Hospital and Research Centre (KFSH&RC).[9]

Where do we go from here? How do we convince patients not to pursue commercial transplantation? More important than just opposing this type of transplantation is to establish a comprehensive plan to meet the increasing demand for kidneys by patients with ESRD. If we fail to do so, then these patients will do whatever in their power to secure kidney donors, including paying living unrelated donors for their kidneys. There will always be a way to circumvent rules and regulations prohibiting the sale of human organs. In addition, we cannot employ what I would like to call "selective ethics" in which we outlaw the sale of human organs in our societies, but somehow look the other way when our patients travel abroad for a paid living nonrelated renal transplantation. This type of medical hypocrisy is unfortunate but not uncommon. If we are so opposed to commercial transplantation on ethical, moral and religious grounds, then what do we do to alleviate the problem of organ shortage? The issue is extremely complex and no one claims to have all the answers to this difficult problem.

In practical terms, the only sources of kidneys that can meet the needs of our patients with ESRD are the relatives, the emotionally related but genetically nonrelated donors, and the cadavers. During the last few years, attempts to increase kidney donation rate in a morally and legally acceptable manner continues to attract professional and public attention. Most of the debate is focused on the following three proposed solutions to the worldwide shortage of cadaveric transplantable organs. First, *presumed consent,* which means that the benefit of the doubt, when no clear evidence of consent to donation is available, goes toward donation, not lack of it. Second, *routine retrieval*, where the consent would simply be subjected to the will of society in a manner similar to compulsive military duty; and third, *financial incentives* for donation.

What then can we do to put an end to commercial transplantation? *First,* I firmly believe that the poor donation record reflected in the Middle East and, for that matter, worldwide, most probably reflects the lack of awareness, trust, and understanding, and is not necessarily inherent in the social and religious belief of the people. This problem is certainly amenable to public education when the issues are clearly and honestly presented, and the discussion involves potential recipients. The discussion should focus on the following items: a) commercial transplantation does not conform to the high ethical standards of our religion; b) it is an illegal practice both in the Kingdom as well as in India. It is, therefore, truly unfortunate to realize that some of our colleagues in the Middle East are involved in commercial transplantation. The teams and hospitals involved in this practice are breaking the law in their own country. This means that the operation will have to be performed underground and in less than desirable circumstances. I believe it is crucial for the Arab Society of Nephrology and Transplantation to establish an unequivocal position pertaining to this issue; c) since the main objective of the teams involved in this practice is one involving profit and not the well-being of the donor or recipient, then corruption and exploitation are likely to prevail and the standards of medical care will undoubtedly be compromised; d) results may be inferior to those of other types of transplant; and e) complications are more common, some life threatening. This is particularly true for the transfer of hepatitis, tuberculosis, and HIV infections. As a matter of fact, we were alarmed to find a high HIV and HbsAg infection rate among the 540 patients transplanted in India (3.7% and 8%, respectively).[11] *Second,* we should convince our patients of the superior overall results of transplants from living relatives. ***Third,*** even if a relative donor is not available, expansion of the already successful local cadaveric transplant programs is a step in the right direction toward meeting their needs. Not only do the people need more education in this regard, but also professionals including residents, intensivists, urologists, neurosurgeons, and nurses. Some potential donors are undoubtedly overlooked during the initial assessment when irreversible brain injury is clearly present. These donors are not usually referred to tertiary care centers, and may not even be resuscitated at the scene of an accident or in primary health care institutions. Furthermore, we should consider expanding the cadaver donor pool by accepting donors less than five years of age, more than 60 years of age, patients with diabetes mellitus, hypertensive and hypotensive patients, those with bacterial and viral infections, and those with a past history of malignancy. *Last but not least,* I think we should no longer hesitate in accepting living emotionally related donors such as spouses and distant relatives. The experience at KFSH&RC and others substantiates the good results achieved from these donors. Furthermore, we must reconsider our objections to accepting donations from close friends with clear altruistic motives.

Having said all this, I recognize that the experience with renal transplantation in Middle Eastern countries, particularly in Saudi Arabia, is encouraging. In this country, we have broken the ice and therefore should not let our success falter. Other Arab countries, especially those with large populations, should also be encouraged by the Saudi experience in cadaveric renal transplantation. If anything, this experience is a lucid example that with determination, cadaveric renal transplant will not remain a dream but can become a reality.

Wajeh Y. Qunibi, MD, FACP
Consultant Nephrologist
Department of Medicine (MBC-46)
King Faisal Specialist Hospital
and Research Centre
P.O. Box 3354
Riyadh 11211, Saudi Arabia

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KIDNEY TRANSPLANTATIONS AT KING FAISAL SPECIALIST HOSPITAL AND RESEARCH CENTRE

Goran Lundgren, MD, PhD; Osman Al-Furayh, MD; Mohammed Akhtar, MD; Yousri Barri, MD;
Hans Collste, MD, PhD; Khalid Al-Meshari, MD; Wajeh Qunibi, MD; Essam Al-Sabban, MD;
Sami Sanjad, MD; Khalid Al-Shaibani, MD; Kirtikant Sheth, MD; Saadi Taher, FRCP

During the five year period from 1987G to 1991G, 161 kidney transplantations were performed at King Faisal Specialist Hospital and Research Centre (KFSH&RC); 79 from cadaveric donors (CD) and 82 from living related donors (LRD). All cadaveric kidneys except one were harvested within Saudi Arabia and 67% were from Saudi nationals. The immunosuppressive protocol was a triple drug regimen comprising cyclosporin-A (CyA), azathioprine (Aza), and prednisone. The actuarial graft survival rates at one and three years were 85% and 76% for the cadaveric donor transplants and 96% and 91%, respectively for the living related donor transplants ($P<0.01$). The corresponding patient survival rates for cadaveric donor transplants (CDTxs) were 97% and 94% and for the living related donor transplants (LRDTxs), 99% and 97% (NS). These results compare well with the best results in the Western world. The most serious surgical complications were vascular thromboses (five cases) and infections of the arterial anastomosis line with bleeding (two cases), all leading to loss of the cadaveric graft. The most common causes of death were virus infection, varicella, cytomegalovirus, and hepatitis B and C. The organ donation rate, from cadaveric donors as well as living related donors, is still low in Saudi Arabia. Lack of organs is the main obstacle to an expansion of this promising transplantation activity. Continuous education of the multinational medical profession as well as the lay population is necessary to improve the situation. *Ann Saudi Med 1994;14(1):5-11.*

The first kidney transplantation (Tx) at King Faisal Specialist Hospital and Research Centre (KFSH&RC) was performed 9 June 1981G. The patient's mother donated the kidney. Eighty-three patients received transplants from living related donors (LRD) until the end of 1986G. The acceptance of the brain death concept by the Council of Islamic Jurisprudence in Amman, Jordan in October 1986G paved the road for initiating a cadaveric kidney transplantation program at KFSH&RC. The first cadaveric transplant (CTx) was performed January 1987G. Here we present the results of the first five years' experience (1987G to 1991G) of CD transplants and compare them with LRD transplants performed during the same time period, with special emphasis on analysis of graft and patient survival, rejection frequency and surgical complications.

Material and Methods

During the above stated period, 79 CD and 82 LRD transplantations were carried out. These constitute consecutive transplants and no patients were excluded from this analysis. Eleven CD and three LRD transplants were retransplantations. Only one recipient of a CD kidney was lost to follow-up 15 months after transplant, when the patient returned to his native country with a well functioning transplant. End of follow-up was 1 April 1992G, providing all patients with a minimum follow-up of three months.

The age, sex, and nationality of recipients and donors are illustrated in Table 1. All except two recipients of CD kidneys and six of LRD kidneys were on maintenance dialysis before transplantation. The etiology of the chronic renal failure was listed as unknown in 53% of the CD recipients and 48% of the LRD recipients due to the fact that the patients often were referred to KFSH&RC at a late stage of their disease when a specific diagnosis could not be established. Only one CD patient and six LRD patients

TABLE 1. *Age, sex and nationality of recipients and donors in living related and cadaveric donor transplantations.*

	Recipient		Donor	
	LRDTx	CDTx	LRDTx	CDTx
Mean age (years)	32.6	28.8	34.1	24.8
< 15 years (%)	10	18	0	30
> 55 years (%)	9	3	6	0
Males (%)	67	62	66	87
Saudi nationality (%)	77	98	77	67

LRDTx=living related donor transplantation; CDTx=cadaveric donor transplantation.

From the Departments of Surgery (Drs. Lundgren, Collste, Al-Shaibani), Medicine (Drs. Al-Furayh, Barri, Al-Meshari, Qunibi, Taher), Pediatrics (Drs. Al-Sabban, Sanjad), Pathology (Drs. Akhtar, Sheth), King Faisal Specialist Hospital and Research Centre, Riyadh.

Address reprint requests and correspondence to Dr. Lundgren: Department of Transplantation Surgery, Huddinge Hospital S-14186 Huddinge, Sweden.

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suffered from diabetes mellitus. The main causes of cadaveric donor brain death were trauma, cerebrovascular accident, and brain tumor (64%, 24%, and 9%, respectively). All cadaveric kidneys except one (from France) were harvested within Saudi Arabia. The different categories of LRDs are illustrated in Table 2.

Surgical procedure: The surgical technique was standard with the exception that in LRD transplants, both the donor nephrectomy and the recipient implantation were performed by the same team, causing a mean cold ischemia time (CIT) of 183 +/- 4.1 minutes (maximum 328 minutes).[1] The mean CIT in CD transplants was 20 hours and 29 minutes (range three hours and 16 minutes to 46 hours and 37 minutes). Eighty percent of CD kidneys and 90% of LRD kidneys had single arteries (P=0.10). In cases of multiple renal arteries, the main artery was usually sutured end-to-end to the internal iliac artery and the smaller artery end-to-side to the external iliac artery or end-to-side to the main renal artery. In three cases where the renal arteries were of about equal size, the renal arteries were sutured together in a V-shape formation and the common lumen was anastomosed end-to-end to the internal iliac artery. In two cadaveric cases, the two arteries were on an aortic patch which was sutured to the side of the external iliac artery. All kidneys were flushed with Euro-Collins solution at +4°C and maintained at this temperature until revascularization. Primary graft function was defined as a spontaneous decrease of the serum creatinine level on the first postoperative day.

HLA typing and matching: The recipients and LRDs were tissue typed in advance. Lymphocytes were isolated from peripheral blood and tested in a modified NIH microlymphocytotoxic assay using commercially available antisera specific for the various HLA A, B, and DR antigens (One Lamdba Co., Los Angeles, CA, USA).[2,3] For emergency typing of cadaveric donors, lymphocytes from mesenteric lymph nodes were preferred. Crossmatching was performed between donor lymphocytes and fresh recipient serum. The T-lymphocytes and B-lymphocytes were incubated at 4°, 22°, and 37° centigrade, respectively for 60 to 120 minutes.[4,5] In patients waiting for transplantation, screening for cytotoxic antibodies (CTA) was carried out regularly using a panel of 36 to 72 donors covering most known HLA antigens. Crossmatches and CTA tests were performed on nonseparated lymphocytes or on cells separated into T and B cells. Sera, which tested positive in a CTA test, were always included in the preoperative crossmatch test in addition to the fresh serum. In the event of a positive T-cell crossmatch, no transplant was performed. Cadaveric kidneys were usually given to recipients with the best HLA-match, provided they were blood group compatible and crossmatch negative. There was no exchange of kidneys between centers on the basis of HLA-matching. No kidneys were discarded because of poor HLA-match.

TABLE 2. *Distribution of living related donors.*

	N	(%)
Parent	15	(18%)
Child	12	(15%)
Sibling	38	(46%)
HLA identical	8	(10%)
HLA 1 haplo mism	21	(26%)
HLA 2 haplo mism	9	(11%)
Other related (grandmother, uncle, nephew, cousin)	17	(21%)

Transfusion policy: Except for a short period in the beginning of 1987G, when a few recipients of LRD kidneys received donor specific blood transfusions, blood was given for medical reasons only. Thirty percent of recipients of CD kidneys and 37% of recipients of LRD kidneys had not received any blood transfusions prior to transplantation. The transfusion data were collected from the patients' charts, dialysis files, and also from questioning the patients.

Immunosuppression and prophylaxis against infections: The basic protocol called for triple drug therapy comprising cyclosporin A, azathioprine, and prednisone. In LRD transplants, the initial daily doses were CyA 8 mg/kg, Aza 2 mg/kg, and prednisone 1.5 mg/kg; CyA and Aza were administered three days prior to surgery. With cadaveric transplants, CyA 3 mg/kg were given orally preoperatively. CyA doses were adjusted to maintain blood levels within the therapeutic range. Prednisone was tapered to 20 mg/d by day 10 post transplant, while Aza was maintained at 2 mg/kg and then lowered according to the WBC. In the presence of postoperative acute tubular necrosis (ATN), CyA doses were maintained at 3 mg/kg and antilymphocyte globulin (ALG) (Lymphoglobuline, Merieux) was administered daily until the serum creatinine fell below 300 µmol/L. CyA was increased three days prior to discontinuation of ALG to ensure therapeutic CyA blood levels. In case of primary graft function, CyA was administered as in LRD transplants. Rejection episodes were treated with bolus doses of methylprednisolone 5 mg/kg for three to four days, followed by tapering to the baseline level over one to two weeks. When the response to methylprednisolone was insufficient, ALG, ATG (Fresenius), or OKT3 (Ortho) was given for seven to 21 days; the duration of treatment was dependent on the response.

Acyclovir (400 mg b.i.d..) and trimethoprim/sulfamethoxazole (80 mg/400 mg q.d.) were given as prophylaxis against cytomegalovirus and *Pneumocystis carinii* infections, respectively, during the first six postoperative months.

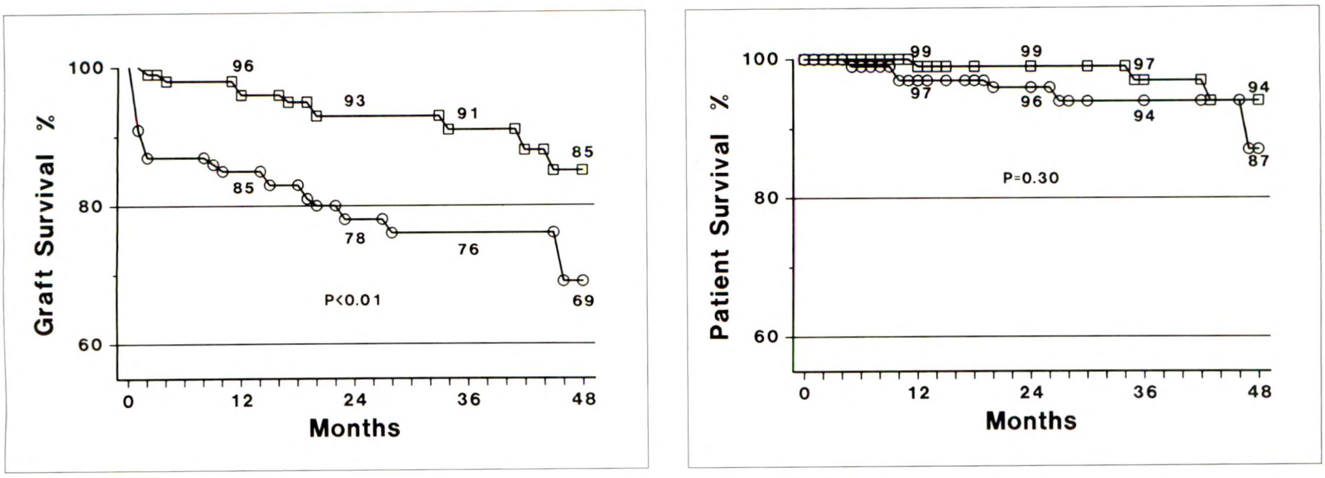

FIGURE 1. Actuarial graft survival (1A) and patient survival (1B) in LRD transplantations (□—□) and CD transplantations (○—○). Figures on curves represent graft survival rates at indicated time intervals.

Statistics: The graft and patient survival probabilities and the free-from-rejection probability were calculated using the Kaplan-Meier method. Patient death was recorded until three months after graft loss. Grafts were recorded as lost when they ceased functioning and also when the patient died with a functioning graft. The log-rank test (Mantel-Haenszel) was used to test the equality of survival and free-from-rejection curves. In the free-from-rejection analyses, patients were censored at the end of follow-up or when the graft was lost for reasons other than rejection. For comparison of proportion of patients in different groups, the chi-square method with Yate's correction was used. A two-tailed Student's t-test for unpaired data was used to compare mean values between groups. Values are given as mean +/- standard error (SE) of the mean .

Results

Survival rates and graft function: The overall graft survival (GS) rates at one and three years were 85% and 76% for the CD transplants and 96% and 91%, respectively for the LRD transplants ($P<0.01$) (Figure 1A). The corresponding patient survival rates for CD transplants were 97% and 94% and for the LRD transplants, 99% and 97% (NS) (Figure 1B). Eighteen CD kidneys and eight LRD kidneys were lost. The causes are illustrated in Table 3. Five recipients of CD kidneys and three of LRD kidneys died (Table 4). Two LRD recipients died from generalized varicella 11 and 34 months after transplantation, and one from CMV after 42 months. There were no deaths during the first four months following surgery.

The mean serum creatinine levels of functioning grafts at one and three years were 135 +/- 7 and 148 +/- 14 µmols/L for the CD grafts and 133 +/- 5 and 136 +/- 6 µmols/L for the LRD grafts, respectively.

Postoperative acute tubular necrosis (ATN): All LRD kidneys had primary function. Thirty-eight CD kidneys (48%) functioned immediately and 37 (47%) had a delayed onset and started on day two to 22. Four CD kidneys (5%) never functioned and were all lost due to vascular thromboses. Fifty CD patients (63%) received post-operative prophylactic treatment with ALG or ATG for one to 27 days because of the tubular injury. The GS rate of immediately functioning CD kidneys was 89% and 86% after one and three years, respectively, compared to 89% and 73%, respectively for the kidneys with delayed function (P=0.45). The four nonfunctioning kidneys were excluded

TABLE 3. *Causes of graft loss.*

	CDTx	LRDTx
Rejection	6	4
Vascular thrombosis	5	
Death	2	3
Wound infection-bleeding	2	
Recurrence of disease	1	1
Biopsy complication	1	
Lymphoma in transplant	1	
Total	18	8

CDTx=cadaveric donor transplantation; LRDTx=living related donor transplantation.

TABLE 4. *Causes of death.*

	CDTx	LRDTx
Infection	2	3
Varicella		2
CMV		1
CMV + Kaposi sarcoma	1	
CMV + Lymphoma in transplant	1	
Liver Failure	2	
Hyperkalemia	1	
Total	5	3

CMV=cytomegalovirus; CDTx=cadaveric donor transplantation; LRDTx=living related donor transplantation.

from this analysis. The mean CIT was 1197 +/- 60 minutes in the group with immediate function and 1213 +/- 62 minutes in the group with delayed function (P=0.86).

Surgical complications: Early (<30 days after surgery) surgical complications are summarized in Table 5. Among the six vascular thromboses encountered in the CD series, two occurred within the first week in kidneys harvested from a seven-month-old donor, one in a kidney with three arteries, and one in a kidney from France with a CIT of 46 hours and 37 minutes. The latter mentioned kidney never perfused well, and the thrombosis was probably secondary to ischemic injury. One arterial thrombosis in a nine-year-old male occurred in the operating room during the ureteral implantation. The thrombus was successfully removed and the graft is still functioning more than two years later. The last thrombosis occurred in a seven-year-old female in whom the arterial anastomosis was re-done because of technical difficulties.

Two renal arteries ruptured after seven and 16 days, respectively. Both ruptures were caused by infection at the anastomotic site, the first with *Staphylococcus aureus* and the second with Aspergillus. The infections were probably transferred from the cadaveric donors. The transplant was removed in both cases.

Five of the six polar infarcts were small and were caused by deliberate ligations of polar vessels which were too small for suturing. The sixth infarct occurred in a LRD kidney, probably already during surgery. The kidney also had a subcapsular hematoma which might have prevented an intraoperative diagnosis. The infarct was visualized on renal nuclear scan and angiography the following day, the infarct comprising just over 50% of the kidney volume. The patient's last serum creatinine level was 148 µmol/L, 20 months after surgery.

The urological complications encompassed four urine leaks and two obstructions, equally distributed between the CD and the LRD series. One leak in each series was corrected surgically by reimplantation into the bladder in one case and by an end-to-end anastomosis to the native ureter in the other. The other two leaks and the two obstructions were successfully managed by ureteral stents.

Some patients had more than one early complication. Therefore, 81% of the CD recipients and 88% of the LRD recipients had a totally smooth complication-free postoperative course.

There were four late (>30 days after surgery) ureteral obstructions, all in the CD series. One was treated by ureteral reimplantation and the other three by balloon dilatation and ureteral stents. A stenosis at the site of the arterial anastomosis was diagnosed in a LRD kidney four months after surgery. This was successfully treated by percutaneous balloon dilatation.

Five vascular thromboses and two arterial ruptures were the only surgical complications leading to graft loss.

Rejection episodes: In the CD series, 50 first rejection episodes, 23 second, 8 third, and 3 fourth rejection episodes were observed and treated. The corresponding numbers in the LRD series were 44 first, 20 second, 8 third, and 5 fourth. The probability of being rejection-free at one year was 38% for CD transplants and 49% for LRD transplants (P=0.33) (Figure 2). In this analysis, an episode of impaired graft function treated with antirejection therapy was considered to be a rejection episode. Data on first rejection episodes are summarized in Table 6. Percutaneous core biopsies were performed in 30% of first rejections in the CD series and in 27% in the living related donor series. All biopsies, except one in the CD series, confirmed the clinical diagnosis of rejection. Fine needle aspiration biopsies (FNAB) were performed in 64% of first rejections in the CD series and in 45% in the LRD series, 75% and 55% of them, respectively, confirming the

TABLE 5. *Early surgical complications.*

	CDTx	LRDTx
Vascular		
Thrombosis	6	
Arterial rupture	2	
Polar infarct	2	4
Postop bleeding requiring evacuation of hematoma	1	1
Urinary		
Leak	2	2
Obstruction	1	1
Other		
Seroma	1	1
Transient paralysis femoral nerve	1	
Re-exploration, no pathology found		1
No complication	64 (81%)	72 (88%)

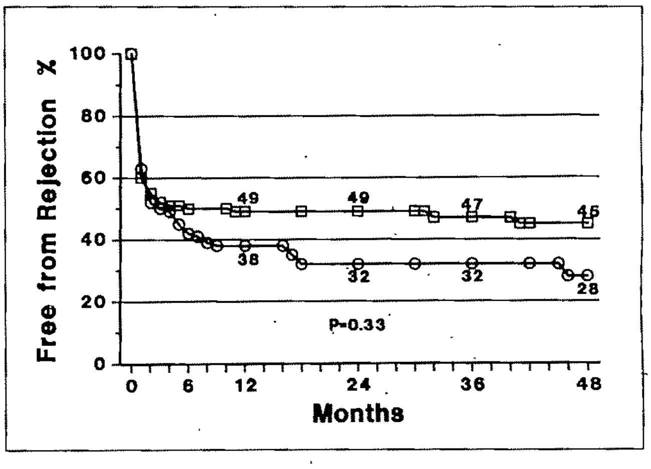

FIGURE 2. Free from rejection analysis in LRD transplantations (□—□), and CD transplantations (○—○). Figures on curves represent the probability of being rejection-free at indicated time intervals.

TABLE 6. *Data in first rejection episodes.*

	CDTx	LRDTx
	n	n
First rejection episodes	50	44
Bx performed	15	12
Bx confirmed rejection	14 (93%)	12 (100%)
FNAB performed	32	20
FNAB confirmed rejection	24 (75%)	11 (55%)
Rejection reversible	48 (96%)	43 (98%)
ALG, ATG and/or OKT3 used	14 (28%)	21 (48%)

CDTx=cadaveric donor transplantation; LRDTx=living related donor transplantation; Bx=biopsy; FNAB=fine needle aspiration biopsy; ALG=antilymphocyte globulin; ATG=antithymocyte globulin.

clinical rejection diagnosis. Only two first rejection episodes in the CD series and one episode in the LRD series were irreversible and led to early graft failure. Twenty-eight (33%) of 84 observed rejection episodes in CD recipients and 29 (38%) of 77 in LRD recipients were treated with antilymphocyte products (ALG, ATG and/or OKT3). Corresponding figures for first rejection episodes were 28% for CD and 48% for LRD transplant recipients. Only six CD kidneys and four living related donor kidneys were lost because of rejection (acute and/or chronic). Experience of a rejection episode had no significant influence on the GS or PS rates, compared to patients without rejection episodes neither in the CD series nor in the LRD series (*P* values 0.37 and 0.38 for the CD and LRD series, respectively). In this last analysis, six CD patients were excluded. These patients lost their grafts during the first seven days for reasons other than rejection.

A retrospective analysis of the validity of the clinical diagnosis of first rejection episodes in the CD series revealed that among 50 episodes, 31 were considered clear, 10 probable, seven as treated on suspicion, and two as probably not being rejections. However, there was no difference in the GS rate between the group of 31 patients with clear rejection episodes and the group with no rejection episodes (P=0.58).

HLA-matching: Complete HLA typing (HLA-A, B, DR in recipient and donor) was available in 59 of the 79 CD transplants (75%). HLA-matching was generally poor. The mean number of mismatches at the A, B, and DR subloci were 1.32, 1.59 and 1.36, respectively and the mean number of shared antigens were 0.57, 0.31 and 0.37. The distribution of transplants with regard to number of mismatched and shared HLA-A+B+DR antigens, respectively, is shown in Figure 3. The GS rate was 100% at end of follow-up in the group of six patients with ≤2 A+B+DR *mismatches* and in the group of eight patients with ≥3 *shared* A+B+DR antigens. Among 14 patients with ≤3 mismatches, one and three year GS rates were 100% and 96% respectively, compared to 82% and 67%, respectively, for patients with higher number of mismatches (P=0.12). When the number of *shared* antigens were analyzed in the same way, the one and three year GS rates were 96% and 90%, respectively, in the group with ≥ 2 *shared* antigens (n=23), and 80% and 61%, respectively, in the group with 0-1 *shared* A+B+DR antigens (n=36) (P=0.04) (Figure 4). There was no correlation between the probability of being rejection-free and HLA-match.

The LRD transplantations were divided into four groups with regard to HLA-match: 1) HLA-identical siblings (n=8); 2) HLA one haplotype mismatches (parents, children, one haplotype mismatched siblings, n=48); 3) HLA two haplotype mismatched siblings (n=9); and 4) donors from outside the immediate family (n=17). The GS rates for these groups are illustrated in Figure 5. There was no statistically significant difference between any of the curves and transplants from donors outside the immediate family did as well as the others.

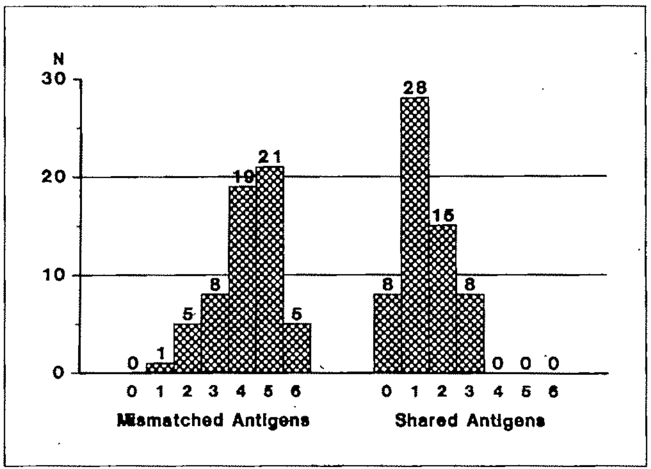

FIGURE 3. Number of mismatched and shared HLA A+B+DR antigens in transplantations from cadaveric donors.

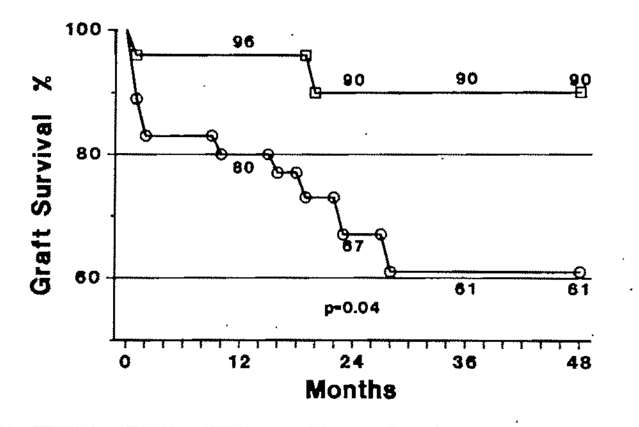

FIGURE 4. Actuarial graft survival in CD transplantations with 0-1 (O—O) and 2-3 (□—□), shared HLA A+B+DR antigens.

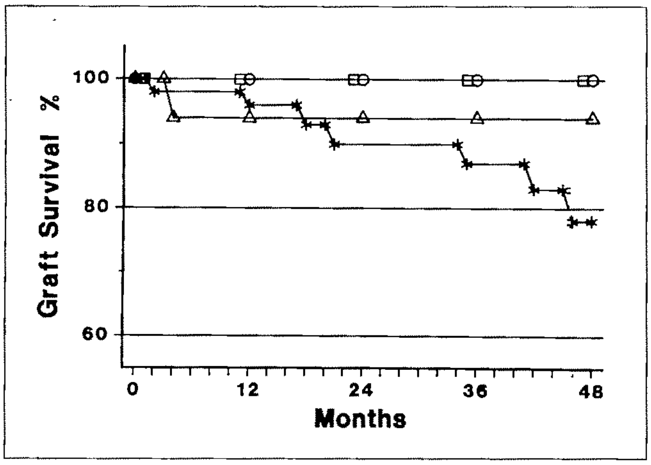

FIGURE 5. Actuarial graft rate survival in different categories of LRD transplantations. □—□, HLA identical sibling donors; *—*, HLA one haplotype mismatched donors; O—O, HLA two haplotype mismatched sibling donors; Δ—Δ, donors outside the immediate family.

Blood transfusions: Thirty percent of recipients of CD kidneys and 37% of recipients of LRD kidneys had not received blood transfusions prior to transplantation. There was no difference in GS rate, PS rate or probability of being rejection-free between transfused and nontransfused patients, neither among CD patients nor among LRD patients. The one and three year GS figures were 85% and 76% for transfused CD patients and 86% and 80% for non-transfused CD patients. The corresponding figures for LRD patients were 96% and 88% for transfused patients and 96% and 96% for nontransfused patients.

Age: No significant difference in GS rate of CD kidneys was seen between various *recipient* age groups, whether the borderline between groups was set at 5, 15, 18 or 29 (median age) years. However, CD kidneys from *donors* ≤ 3 years old had a significantly lower GS rate than kidneys from donors older than three years (P<0.0001). Four of five kidneys from children ≤ 3 years of age were lost, two due to vascular thrombosis and two due to rejection. Among CD recipients who received kidneys from donors older than three years of age, the one and three year GS rates were 89% and 82%, respectively.

Discussion

This study demonstrates that CD transplants utilizing locally harvested kidneys, and LRD transplants, can produce the same excellent results in the Middle East as in the Western world.[6-8] This is encouraging, since kidney transplantation, which is substantially less costly than maintenance dialysis, ought to be the predominant treatment of chronic renal failure in developing countries with limited economical resources.[9,10] Contributing factors to our fine results may be the relatively low donor and recipient mean age and the low number of recipients suffering from diabetic nephropathy. Although it is true that no correlation was found between recipient age and GS in this series, this may well be explained by the low number of elderly patients (>55 years of age). With lower recipient age follow fewer cardiovascular complications, less arteriosclerosis in the iliac vessels used for anastomoses with fewer technical difficulties, and probably a higher tolerance to immunosuppression. It was interesting to note that no patient in this report died from cardiocerebrovascular disorder, which is the leading cause of death in most transplantation materials in the Western countries.[11,12] On the other hand, two LRD recipients died from varicella with well-functioning grafts. In order to reduce this unnecessary loss of lives and grafts, we have initiated a pretransplantation vaccination program for recipients who lack antivaricella zoster antibodies. Two patients died in liver failure. This reflects another serious problem in Saudi Arabia where the frequencies of HBsAg and HCV carriers are high, which leads to a high incidence of chronic active hepatitis among our dialysis and transplant patients (to be discussed in another article).[13]

The inferior results with cadaveric kidneys from donors <3 years of age is in accordance with other reports[14-16] although some authors have experienced a high success rate also with these organs.[17,18] The technical problems with these small vessels are obvious. Transplantation of both donor kidneys en bloc avoids this problem and might be considered if donors <3 years of age are used.[19] We performed one en bloc transplantation from a three-year-old donor but the organs rejected within two months in a patient with multispecific antibodies.

Only 48% of the CD kidneys had an immediate function. This relatively low figure may be partially explained by the rather strict definition of primary function. Many authors define primary function as absence of need for postoperative dialysis, which obviously will increase the figure for primary function.

The rejection frequency in this material was unusually high, only 38% of CD recipients being rejection-free at one year. In spite of the high rejection frequency, which may be related to the low recipient mean age,[20,21] only six CD and four LRD kidneys were lost due to acute and/or chronic rejection. Furthermore, there was no correlation between experience of rejection and poor GS. This is in contrast to the experience of other authors[20,22] who found a rejection episode to be the strongest indicator of poor GS. The explanation for these discrepancies may be the rather heavy antirejection treatment many patients were exposed to in this series, including the rather abundant use of antilymphocyte products. Treatment with ATG and/or OKT3 has been reported to be associated with a high morbidity and mortality rate from CMV infections, especially in older patients.[23-25] Centers treating such patients may therefore abstain from repeated antirejection treatments, which result in more rejections leading to graft loss. Our younger patients tolerated immunosuppression better and the higher immunosuppressive load might have reversed more rejection episodes and might also have facilitated the induction of chimerism, and thereby a state of "tolerance", which recently was found by Starzl et al to exist in many solid organ recipients with prolonged graft function.[26]

A surprising finding was the correlation between HLA-matching and GS in the CD series, especially considering the limited material. Such a correlation was reported in large multicenter materials[6,27,28] but was usually absent in smaller multicenter[29,30] and single center studies.[31] Also in large materials, a beneficial effect of HLA-matching was usually most evident with high degrees of HLA-matching.[6,27] The absence of a blood transfusion effect is in accordance with most reports during recent years[29,32] and it is probably generally agreed upon today that pre-transplantation blood transfusions should be avoided.[33]

The major obstacle to transplantation in Saudi Arabia is the low donation rate from CD as well as LRD. In 1992G, 3212 patients were on maintenance dialysis within the Kingdom, and only 129 transplantations (64 from CDs and 65 from LRDs) were performed during 1991G. The low donation rate and the prolonged waiting period for transplantation compel many patients to travel abroad to either have CD transplantation or to purchase kidneys from nonrelated individuals. This practice further reduces the incitement for donation within Saudi Arabia. To improve this situation, continuous education is necessary for the multinational medical profession as well as the lay population - a formidable task in Saudi Arabia, but a task the Kingdom shares with most other countries.

Acknowledgment

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SEASONAL VARIATION OF CULTURE POSITIVE BRUCELLOSIS AT A MAJOR TEACHING HOSPITAL

Saleh R. Al-Ballaa, FRCP(C); Suliman R. Al-Balla, FRCP(C); Abdulkarim Al-Aska, Facharzt;
Abdelmageed Kambal, FRCPath; Mogbil A. Al-Hedaithy, FRCP(C)

Brucellosis is one of the main zoonoses in the world. In Saudi Arabia, it was recognized as a major health problem in 1983G and since then many measures have been implemented to control the disease. We conducted a study to determine the yearly incidence and seasonal variation of blood culture positive brucellosis (Brucella cases) diagnosed at King Khalid University Hospital (KKUH) in Riyadh between 1985G and 1991G. The results showed that there was a fivefold decline in the incidence of Brucella cases over the seven years of the study from 8.6 cases/1000 admissions in 1985G to 1.4 cases/1000 admissions in 1991G. The disease showed a prevalence that extended throughout the year with the majority of cases occurring during spring, summer and early fall. The possible reasons for the seasonal variation and decreasing incidence of brucellosis noted in this study are discussed. *Ann Saudi Med 1994;14(1):12-15.*

In spite of the growing number of countries declared brucella-free, the disease remains one of the main zoonotic infections throughout many parts of the world with major economical and public health implications.[1]

About 500,000 new cases occur annually worldwide, with predominance in the Middle East, the Mediterranean countries, South America and Central Asia.[2,3] The first indication that the disease exists in Saudi Arabia appeared in the ARAMCO Epidemiology Bulletin, the 15th week issue of 1968G;[4] since then, sporadic cases have been reported in the literature.

The disease was only recognized as a major public health problem in 1983G when Kambal et al reported their experience with brucellosis in Riyadh, Saudi Arabia.[5] This report stimulated the initiation of many projects to study the clinical aspects and epidemiology of the disease.[6-20] One such project was a countrywide, cross-sectional survey of 23,000 randomly selected subjects. The results of this survey indicated a high exposure rate of 35% and an active disease in 2% of the population screened.[10] The government, recognizing the magnitude of the problem, has adopted a brucella control program focused on the eradication of this disease. This comprised public education and mass vaccination of livestock. No data is yet available on the trend of incidence of brucellosis over the last few years in Saudi Arabia. We conducted a study to determine the yearly incidence and seasonal variation of blood culture positive brucella cases over a seven year period.

Material and Methods

King Khalid University Hospital (KKUH) is a 630-bed teaching hospital which provides both primary and tertiary care. The microbiology laboratory records of the hospital were retrospectively reviewed over a seven year period from 1 January 1985G to 31 December 1991G.

The total number of blood cultures performed and the number of positives for different organisms were determined for each month. To evaluate the trend in incidence of blood cultures positive for *Brucella species* in relation to other organisms, the annual number of positive blood cultures for *Brucella species* was compared to that for the other three most common pathogens identified: *Staphylococcus aureus, Escherichia coli,* and *Klebsiella species.*

For the analysis of incidence and seasonal variation of brucella cases, patients with multiple blood cultures were included only once, at the time of the initial positive blood culture.

Laboratory Methods: Each set of blood cultures consisted of two bottles, one BACTO Tryptic soy broth w/sps and CO_2 incubated aerobically and one BACTO Thiol broth w/sps and CO_2 incubated anaerobically (Difco Laboratories, Detroit, MI, USA).

Each bottle was promptly inoculated with 5 ml of blood collected under aseptic conditions by medical staff and by phlebotomists. The media was incubated at 37°C and observed daily for signs of microbial growth such as turbidity, gas formation or hemolysis.

After two and seven days of incubation or at any time signs of microbial growth were detected, gram stain and subculture onto chocolate and two blood agar plates were done. MacConkey agar plate was also inoculated if gram

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From the Department of Medicine, King Saud University, Riyadh.

Address reprint requests and correspondence to Dr. Saleh R. Al-Ballaa: Assistant Professor, Department of Medicine (38), College of Medicine, King Saud University, P.O. Box 2925, Riyadh 11461, Saudi Arabia.

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stain showed the presence of microorganisms. The chocolate and one blood agar plate were incubated in a CO_2 incubator, the MacConkey agar plate under aerobic conditions and the other blood agar plate in a gas pack jar (BBL, Becton Dickenson Microbiology Systems, Cockeysville, MD, USA), all at 37°C for 48 hours. If brucella culture was ordered or suspected from history, the aerobic bottle was reincubated for a total of eight weeks and subcultured weekly onto blood and chocolate agar plates. The microorganisms were identified according to the procedures described in the manual of clinical microbiology.[21] The slide agglutination test for brucella was performed using the Wellcome nonspecific *Brucella abortus* and *Brucella melitensis* agglutinating serum (Wellcome Diagnostics, Dartford, England).

Results

Between 1 January 1985G and 31 December 1991G, a total of 46,931 blood cultures were processed in KKUH microbiology laboratory. Out of these, 1036 cultures obtained from 728 patients were positive for *Brucella species*. The incidence of blood cultures positive for *Brucella species* progressively declined over the seven years of the study from a peak of 54.5/1000 blood cultures performed in 1985G to 6.5/1000 blood cultures in 1991G (Figure 1). This microorganism was the most common pathogen isolated from blood between 1985G to 1988G but regressed to the fourth in 1991G.

In contrast to the sharp and progressive decline of *Brucella species* as a cause of positive blood culture, the incidence of the other three most common pathogens identified: *S. aureus*, *E. coli* and *Klebsiella species* remained relatively constant over the same period (Figure 1).

The incidence of brucella cases decreased from 8.6/1000 admissions in 1985G to 1.46/1000 admissions in 1991G ($P<0.0001$). This represented more than a fivefold decline in incidence (Figure 2). Analysis of the number of cases diagnosed each month over the seven years of the study demonstrated that although the disease was found to be prevalent throughout the year, a predominance of cases occurred during the spring, summer and early fall compared to late fall and winter (Figure 3). The largest number of cases were diagnosed during July with an average of 15.4 cases/month and the lowest number during November to February with an average of <6 cases/month ($P<0.0001$). Most noticeable was that members of the same family would frequently present with a culture-positive brucellosis within a few days of each other and occasionally on the same day.

During the seven year period, there were six cases of hospital-acquired brucellosis; four of which were acquired in the microbiology lab and were previously reported,[22] the

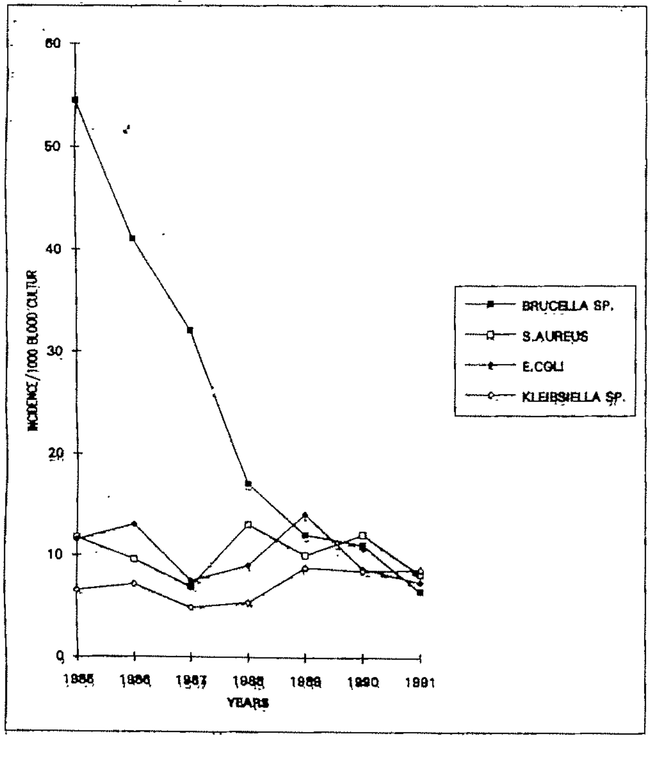

FIGURE 1. Incidence of the four most common pathogens isolated/1000 blood cultures.

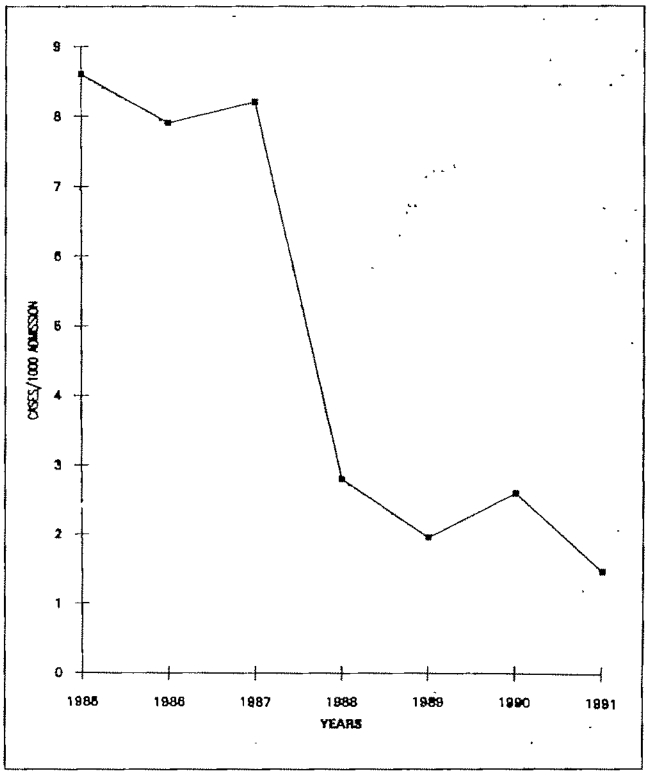

FIGURE 2. Incidence of brucella cases/1000 admissions.

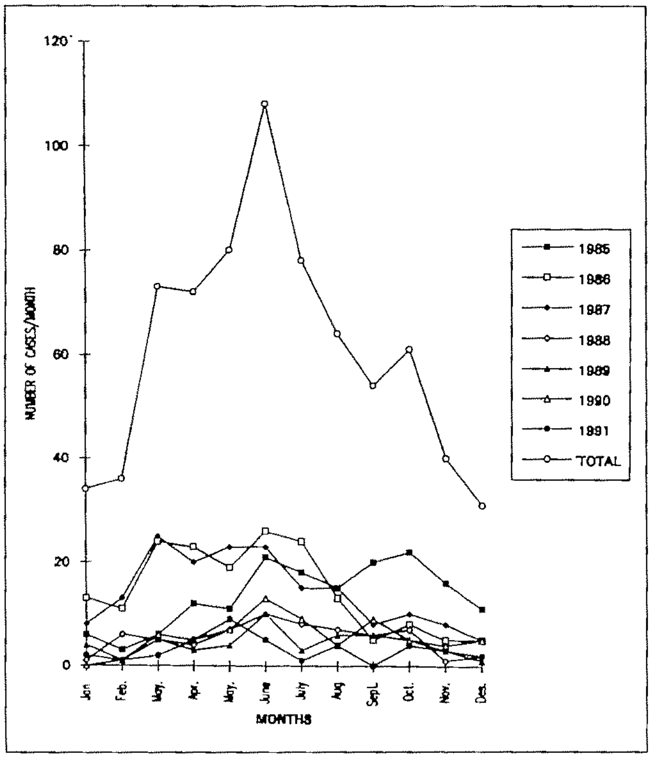

FIGURE 3. Seasonal variation of brucella cases from 1985G to 1991G.

remaining two were acquired in the research laboratory by staff members conducting a study on *Brucella species*. This represents 0.8% of all cases in the study. Since 1987G, no such incidents occurred in these laboratories.

The table indicates the number of blood cultures performed and the number of patients admitted to the hospital each year between 1985G and 1991G.

Discussion

The incidence of brucellosis diagnosed in KKUH has declined fivefold over a seven year period from 8.6 cases/1000 admissions in 1985G to 1.4 cases/1000 admissions in 1991G. During the same period, the laboratory procedures and the media used for blood cultures remained the same, indicating that the change in incidence observed is most likely related to a decrease in the number of brucella cases presenting to the hospital. It is difficult to ascertain with certainty the reason for this change. One possibility is that the increased awareness of the disease among health care providers in other centers coupled with improved diagnostic techniques may have resulted in the detection and treatment of a higher proportion of brucella cases that would otherwise have presented to our hospital. The control measures in effect, including public education, pasteurization of dairy products and immunization of livestock may, in addition, have contributed to the decline in brucella cases seen at our hospital.

TABLE : *Number of admissions and blood cultures per year.*

Year	Number of Admissions	Number of Blood Cultures
1985	18,692	4,507
1986	22,164	6,459
1987	21,142	7,188
1988	22,654	6,127
1989	24,615	6,262
1990	26,763	8,233
1991	25,990	8,155

Analysis of the seasonal variation of brucellosis showed a prevalence that extended throughout the year with the predominance of cases occurring during spring, summer and early fall. The early summer coincides with the highest season of parturition and increased milk production among domestic animals. During the other two periods, spring and fall, the weather in Saudi Arabia is mild and many people are in the habit of camping in the desert where they may be exposed to *Brucella species* through contact with infected animals, contaminated environment and/or by actually drinking infected raw milk. Similar seasonal variation was previously documented by other investigations.[6,12] The observation that, on many occasions, members of the same family presented within a few days of each other with brucellosis is very suggestive of a common source of exposure. This can occur during camping in the desert or when infected raw milk is brought to the household for family consumption.

During the seven years of the study, 728 cases of brucellosis were diagnosed in our laboratory. Only six cases (0.8%) acquired the disease in the laboratory.

Accidental exposure to *Brucella species* is a serious threat to laboratory personnel, especially those working in endemic areas. The disease was previously documented as the most common cause of laboratory acquired infection.[23] It is estimated that between 1% to 2% of cases of brucellosis in the USA result from exposure to the organism in microbiology and research laboratories.[2]

It is vital that strict containment procedures are implemented in research and microbiology laboratories in an effort to prevent such incidents. In our center, no laboratory-acquired brucellosis occurred during the last four years.

In conclusion, this paper provides an indication that the incidence of culture positive brucellosis at King Khalid University Hospital is declining. We emphasize the need for further work to continuously monitor the incidence of this disease in the Kingdom of Saudi Arabia and to intensify the control measures currently being used.

Acknowledgment

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NEONATAL HIP INSTABILITY IN SAUDI ARABIA: RESULTS AND COST EFFECTIVENESS

Khalid Al-Umran, MD

The benefits of screening hips at birth for congenital dislocation have been repeatedly confirmed but doubts have been raised about the need for splinting all positive cases. Experience from an ongoing screening program, now in operation for over 11 years, is presented particularly with reference to cost benefit of screening and early surgical intervention. Of 30,651 live born babies screened for congenital dislocation of the hip (CDH) employing Barlow and Ortolani maneuvers, 132 were found to be positive, giving an incidence of two to six per 1000 live births, averaging 4.3/1000 for the period. The implications of epidemiologic and clinical observations and of management have been discussed. The cost of screening and of surgical management of cases that would not have stabilized without splinting has been resolved, even assuming that three of four positive cases might have stabilized without intervention. Cost effectiveness of a screening program for CDH was observed from this 11 year study, fully justifying a sustained program apart from the human misery an overlooked diagnosis may cause. *Ann Saudi Med 1994;14(1):16-18.*

An unstable hip at birth can bring untold misery to a child and his/her family and impose avoidable expenditure on later surgical intervention. Experiences in the Eastern Province of Saudi Arabia are evidence in point.[1,2] The benefits of screening are substantial and very few cases are overlooked at birth if a sustained screening program is in operation.[3] Routine screening of all neonates at the King Fahd Hospital of the University (KFHU) began in 1982G, with the necessary cooperation between the Departments of Pediatrics and Orthopedics in the diagnosis and management of neonates with unstable hips. This communication presents its experience of an 11 year study of an ongoing screening and early intervention program with special reference to cost effectiveness.

Patients and Methods

All babies delivered at the KFHU, Al-Khobar, Saudi Arabia since 1 January 1982G have been examined routinely for hip instability employing the Barlow and Ortolani maneuvers. This examination is carried out within 24 hours of birth. Confirmation of a positive screening test is determined by an orthopedic surgeon.

Radiologic examination is not carried out routinely. A von Rosen splint is applied to those positive on screening with necessary written and verbal instructions to the parents, and followed up by an orthopedic surgeon. After six to 10 weeks, the splint is removed, with further follow-up at three, six and 12 months (x-ray films taken at three and 12 months). For statistical analysis of the results, the chi-square test has been used.

Results

During the 11 year study, a total of 30,651 live births were subjected to screening for hip instability as described. The yearly breakdown between 1982G and 1992G is shown in Table 1. Of the 30,651 babies, 132 were positive, giving a yearly incidence varying between 2.0 and 6.0/1000 live births, averaging 4.3/1000 for the period. The sex ratio was 1:3.7, the female predominating. Of the 132 babies positive on screening, three were small, 109 appropriate and 20 large for gestational age. Eighteen babies were delivered by breech (13.6%). The distribution of hip instability with respect to sidedness and sex appears in Table 2. A positive family history (first degree relatives) could be obtained in nine (6.8%) babies. Additional deformities observed in 19 (14.4%) babies were talipes equinovarus, congenital heart disease, microcephaly, meningocele, hypospadias and inguinal hernia (Table 3). Ninety-nine cases (74%) could be followed up to the age of walking. No complications were observed except minor skin irritation from the splint; one case required surgical intervention resulting from noncompliance by the parents. None of the positive cases returned after the follow-up period to report any hip problem.

Discussion

The yearly incidence of congenital hip dysplasia in this region averages 4.3/1000 live births with a range of 2.0 to 6.0/1000 as determined by a large study of 30,651 babies examined between 1982G to 1992G. Considering the

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Address reprint requests and correspondence to Dr. Al-Umran: Associate Professor and Chairman, Pediatric Department, King Faisal University, P.O. Box 40140, Al-Khobar 31952, Saudi Arabia.

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TABLE 1. *Annual incidence of neonatal hip instability in deliveries at the KFHU, 1982-1992.*

Year	Live Births	+ve Cases	Incidence/1000
1982	2012	4	2.0
1983	2394	10	4.2
1984	2630	14	5.3
1985	2817	16	5.7
1986	2842	17	6.0
1987	2855	11	3.8
1988	3017	10	3.3
1989	3154	13	4.1
1990	3148	15	4.8
1991	2549	5	2.0
1992	3233	17	5.3
Total	30651	132	4.3

KFHU=King Fahd Hospital of the University; +ve=positive.

TABLE 2. *Sex and side of defect in unstable hips.*

	Bilateral	Right	Left	Total
Female	23	29	52	104
Male	14	5	9	28
Total	37	34	61	132

TABLE 3. *Incidence of anomalies in 132 cases associated with unstable hips.*

Anomalies	Number of Cases
Talipes equinovarus	7
Congenital heart disease	3
Microcephaly	2
Meningocele	3
Hypospadia	2
Inguinal hernia	2
Total	19 (15.4%)

varying incidences in different regions of the world from 2.5 to 20/1000, the incidence of 4.3/1000 cannot be considered high as has been suggested.[3] Consanguineous marriages, which are common in Saudi Arabia,[4] would not appear to be the major causative factor, since some regions of the world where such marriages are uncommon have higher incidences of unstable hip.[3,5,6] Predominance of female babies,[8] higher frequency of involvement of the left hip[9] and of breech deliveries appear to be common denominators as reported here and in other studies.[8,10-12] Whereas both high and low birth weights have been shown to increase the risk for hip instability,[10] prevalence of hip dislocation and other congenital anomalies in first degree relatives was significantly higher in the present series.

The fact that no baby (apart from five during the initial year of study) in the follow-up service of the screening program was found to present later with hip dislocation may testify to the efficiency of the splinting procedure. However, the cost effectiveness of sustaining the program should be reviewed in the light of doubts raised about the need for splinting all positive cases.[13] It has also been suggested that the head of the femur and the ligaments of the knee could be damaged if the screening is not carried out gently. Despite reports of hip joint damage following splintage,[14] this has not been a problem in the population presented in our study. No case of femoral head necrosis was observed using the von Rosen splint.[1]

It is suggested that three to five babies may be splinted unnecessarily for every one benefiting from the procedure.[2,15] Yet considering: a) the serious long-term morbidity in overlooked cases; b) the poor results of late intervention; and c) the lack of complications and minor inconvenience of the splintage, it may be argued that the screening and management program should continue. From the viewpoint of health care costs, assuming that one of four cases would not have stabilized without splinting, 33 of the 132 positive cases would have required surgery. Allowing conservatively for a six week stay in hospital per child at SR 1000 per day, total hospitalization costs for the 33 cases would have been approximately SR 1.4 million. This figure does not include bilateral cases and cases where the diagnosis is delayed two to three years or more, where hospitalization periods may be longer. Also excluded are the actual surgical and transportation expenses for the relatives to and from the hospital with associated loss of work time. In contrast to costs of hospitalization, screening/splinting programs are cheap. In this study, the screening of 30,651 cases over the 11 year period (average eight per day) incurred estimated salary costs of SR 40,000 based on two minute examinations per infant. Added to this was the cost of splinting the positive cases (132) at SR 200 per splint, amounting to SR 26,400 and of radiographic costs at SR 50 per patient amounting to SR 6600 - total SR 73,000. Cost of screening, splinting and radiography (SR 73,000) totals approximated 5% of the cost of surgery (SR 1.4 million) for those cases expected to deteriorate without splinting. Thus, the tremendous cost effectiveness and prevention of suffering and misery of the child and his parents leave little doubt as to the necessity of sustaining the program as an essential public health service.

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DEVELOPMENT OF SUBCUTANEOUS ABSCESSES DUE TO *MYCOBACTERIUM BOVIS* FOLLOWING HEPATITIS AND BACILLUS CALMETTE-GUERIN VACCINATION

Ghazala Kafeel, MD; SM Hussain Qadri, PhD, FRCPath, Diplomate ABMM, FAAM;
S. Abdul Khadir Pasha, MS, MCH; VS Akbar Sharif, MS, MCH; SM Ishrat Shakir, MS

Vaccination to prevent hepatitis B and tuberculosis (TB) forms a part of the national immunization program in the Kingdom of Saudi Arabia. The hepatitis B vaccination was introduced in the Makkah region in January 1991G. Since then, 25 children have developed post vaccination subcutaneous abscesses at the site of vaccination. Microbiological studies proved these to be of bacillus Calmette-Guerin vaccine (BCG) origin. Ten patients were treated successfully with isoniazid (INH) and rifampicin and 15 with INH alone. Four patients required incision and drainage. Possible reasons for this complication in our patients are discussed. *Ann Saudi Med 1994;14(1):19-21.*

Vaccination of infants with bacillus Calmette-Guerin vaccine (BCG) and hepatitis vaccine for the primary prevention of tuberculosis (TB) and hepatitis B is now practiced in many countries, including Saudi Arabia. Hepatitis vaccine was included in the immunization schedule in the Makkah region in January 1991G. According to recommendations, the first dose of hepatitis vaccine is given at birth intramuscularly in the thigh. On the same day, BCG is also given intradermally in the deltoid region. Subsequent doses of hepatitis vaccine are given over the next five months. Local complications following BCG, such as abscess formation and adenitis, are well known and amount to less than 2% of the vaccinated individuals.[1-4] Local complications following hepatitis vaccine are not described. We report 25 cases of post vaccination subcutaneous abscesses in the thigh, the site of hepatitis vaccination.

Patients and Methods

Patients: Twenty-five children attending Al-Noor Specialist Hospital, Makkah during 1991G to 1992G (1411H to 1412H), developed post vaccine abscesses; 19 of these were Saudi nationals. Male to female ratio was 2:1 and all were between 1.5 to 13 months of age, except for a seven-year-old male. The latter child had symptoms following booster in the thigh. These children had received hepatitis vaccine (Engerix-B, Smith Kline) from various vaccination centers in Makkah.

Clinical Findings: The patients presented with 4 cm to 10 cm diameter, fluctuant, nontender, diffuse swelling of the thigh at the site of the hepatitis vaccine. Fever, regional lymphadenopathy, skin involvement or any constitutional symptoms were absent. All presented with a BCG scar in the deltoid region. Twelve patients developed abscesses after the first injection of hepatitis vaccine while in others, abscesses were formed following the other two doses. The swelling with insidious onset was observed from one to four weeks following the injection. Family history of tuberculosis was absent.

Laboratory Investigation: Erythrocyte sedimentation rate (ESR) ranged between 25 mm to 40 mm/first hour. Chest x-ray was normal and tuberculin test was positive in all, ranging from 10 mm to 13 mm. Diagnostic needle aspirations yielded 10 ml to 15 ml of cream colored pus composed of neutrophils, lymphocytes and occasional epithelioid granulomata in a caseous background. Acid-fast bacilli were seen in all the specimens as long filamentous organisms by Ziehl-Neelsons stain. Biopsy material available in 11 cases showed caseating epithelioid granulomas. Routine bacteriological cultures were sterile. Cultures for acid fast bacteria (AFB) in the Mycobacteriology Laboratory of King Faisal Specialist Hospital and Research Centre (KFSH&RC) grew *Mycobacterium bovis* which was susceptible to streptomycin, isoniazid (INH), rifampicin, and ethambutol but resistant to erythromycin. Culture studies were conducted on 19 specimens of which only two did not yield any microbial growth. Several batches of hepatitis vaccine were also cultured but did not show any microbial growth.

From Al-Noor Specialist Hospital, Makkah (Drs. Kafeel, Pasha, Sharif, Shakir); and Department of Pathology (Dr. Qadri), King Faisal Specialist Hospital and Research Centre, Riyadh.

Address reprint requests and correspondence to Dr. Qadri: King Faisal Specialist Hospital and Research Centre, Department of Pathology (MBC-10), P.O. Box 3354, Riyadh 11211, Saudi Arabia.

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Cultures of the BCG vaccine grew *Mycobacterium bovis* with the same sensitivity pattern as that in the patients.

Management: Since culture facilities for AFB were not at hand at Al-Noor Specialist Hospital, the first 10 cases were treated as tuberculosis abscesses by surgical intervention and two by drug regimen (INH plus rifampicin) for nine months on the basis of clinical and laboratory data. Complete healing of the wound was noted within a period of two to four weeks with no recurrence one year following completion of treatment. The aspirated material from these and other patients was sent to the Mycobacteriology Laboratory of KFSH&RC and grew *M. bovis*. After the identification of the organisms, the remaining cases were treated as BCG abscesses by repeated (weekly or biweekly) aspirations and INH therapy for six months. The lesions took two to three months to heal completely with no recurrences in six months' follow-up period. Four of these 14 cases required incision and drainage as the abscess began pointing on the surface.

Discussion

Although post vaccination abscess formation has been reported previously,[5,6] a uniform management schedule is not available for BCG abscesses, possibly because of low prevalence ranging from 0.0001% to 1.5% of vaccine.[2,3,7] Most of the reports are not well documented by microbiological studies or consist of small groups of cases only. A report on 18 cases with abscess formation from Zaire showed AFB positivity in 75% while *M. bovis* was isolated from 63% of patients.[8] Murphy et al reported the management on two culture-proven cases,[9] while culture data were available in only two of 18 cases reported by Hanley et al.[10] In our series of 25 cases, AFB positivity was 100% by staining; culture studies were possible in 19 cases of which 17 (89.5%) grew *M. bovis*. The two negative results could possibly be due to a delay of more than six months between specimen collection and culturing. However, all the eight cases without culture or negative microbiological report showed AFB on the smears and caseating epithelioid granulomata on histology.

The first group of 10 cases were treated as tuberculosis abscesses by surgical intervention and two by drug regime. Once the organisms were identified, subsequent cases were treated as BCG abscesses by aspirations and INH therapy. de Souza et al reported a rapid resolution (30 days) in 19 of 27 cases on systemic INH therapy.[3] A rapid resolution was also seen in our cases but complete recovery required two to four months. In the majority of cases, we neither saw any advantage of a two drug regimen over one nor surgery over chemotherapy. Our isolates were resistant to erythromycin, unlike a number of other reports.[7,8,10,11] Trials with aspiration alone are underway.

It is well known that BCG vaccine, when injected beyond the dermal plane, results in abscess formation as seen commonly after BCG vaccination.[5,6] We found that all of our patients had identical lesions in the subcutis of the thigh where hepatitis vaccine was said to have been given. In the absence of a primary focus, cutaneous involvement or any disseminated disease, the only possibility is that the organisms were introduced with the hepatitis vaccine or a wrong injection was given. Possibility of a contaminated vaccine is unlikely since only 25 cases were encountered over a period of two years. Batch number of the vaccines used was not on the record. Random cultures of the hepatitis vaccine samples did not grow any microorganisms.

Technical error appears to be the most likely cause of the post vaccine abscess formation. The nature of this error is difficult to assess. However, the problem started only after hepatitis vaccination was introduced with the BCG vaccination in the immunization schedule. Sporadic use of a common syringe for injecting both BCG and Engerix-B can be considered as a possibility. We ruled out the likelihood of the two vaccines being mixed up because the BCG vaccine comes in an ampule while the hepatitis vaccine is dispensed in vials. Since BCG scar was present in all these cases, the possibility of mixing up of vaccines arises only when the syringes are preloaded to vaccine a number of children at the same time.

If the above hypotheses are true, an explanation is needed for those cases developing the lesion after the second and the third dose of hepatitis vaccine. In some, but not in all cases, subsequent injections had only attracted attention towards the pre-existing lesion. In one child, the hepatitis vaccination was deferred for one month because of neonatal jaundice and an abscess appeared after the vaccination. The seven-year-old male was given a booster dose of hepatitis vaccine alone.

Detailed interview of the technical staff proved fruitless. Any single person responsible for mix-up cannot be considered because the patients received the vaccines from different vaccination centers in Makkah. We believe that if this can happen in a number of centers in one city, it can also occur in other places. An active surveillance may help in arriving at the root cause of this problem. A reorientation program for the vaccination staff is absolutely essential and is underway. Proper recording of batch numbers of the vaccine used is equally essential to detect any defect in the vaccine. Spacing of the BCG and hepatitis vaccination remains an attractive alternative.

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A PROSPECTIVE STUDY OF THE MORBIDITY PATTERN OF PATIENTS SEEN AT A UNIVERSITY PRIMARY CARE CLINIC

Sulaiman A. Al-Shammari, MBBS, MSc, MRCGP(UK); Jamal Saleh Jarallah, MSc, MRCGP(UK);
Itunu Olusola Olubuyide, BSc, MBBS, MD(Bristol); Elijah A. Bamgboye, BSc, PhD(London)

Information on the morbidity pattern of patients seen at a primary care clinic is sparse or not available for most countries in the Middle East including Saudi Arabia. A prospective study of all new patients at the primary care clinic of King Khalid University Hospital (KKUH), Riyadh, Saudi Arabia was therefore carried out over a period of one year (1991G to 1992G). An analysis of the morbidity pattern of 9,441 new patients seen over this period is hereby reported. There is a male preponderance overall and more than 70% of the patients were below 40 years of age. Ill-defined illnesses, diseases of the skin, genitourinary, digestive, musculoskeletal and respiratory diseases accounted for more than 70% of the patients. About one-third of the patients, mainly those with diseases of the skin and genitourinary systems, were referred for specialist care. It is conceivable that the commonly observed pattern of diseases in this study may change over a period of time either due to the interventions adopted by the primary care clinics or as part of social development or as a cumulative effect of both. The primary physician has to be aware of such a change by periodically analyzing the available morbidity pattern. *Ann Saudi Med 1994;14(1):22-25.*

Primary care has expanded dramatically in the Kingdom of Saudi Arabia during the past two decades[1] due to the rapid socioeconomic development of the country. However, considerable gaps still exist in the knowledge of the morbidity pattern of the patients at the Primary Care Clinic (PCC). Yet such knowledge remains one of the ways of ascertaining the true status and significance of diseases in the health profile of the community. It is with this objective that the progressive study was undertaken.

Patients and Methods

The study was conducted at the PCC of King Khalid University Hospital (KKUH), Riyadh, Saudi Arabia between May 1991G and April 1992G inclusive. The hospital caters to Saudi citizens from all over the Kingdom and also provides treatment to expatriates. The PCC is designed for patients 12 years and older while a similar clinic for children is also in operation in the hospital. There was an accurate census of the total number of patients attending the PCC during the period of the study and all the new patients were studied. They were subjected to a detailed medical history and clinical examination and were investigated appropriately. The age, sex and nationality of each patient were recorded and the principle diagnosis was coded in accordance with the ninth edition of the International Classification of Diseases.[2] Where a diagnosis could not be determined, the most important clinical feature was recorded for the patient.

Results

Within the one year period of this study, 65,789 patients, of which 9,441 (14.4%) were new patients, were seen in the PCC. The age, sex and nationality distribution of the patients are presented in Table 1. Saudis comprised

TABLE 1. *The age, sex and nationality distribution of patients at the Primary Care Clinics of King Khalid University Hospital, Riyadh.*

Characteristics	Frequency (n=9441)	(%)
Age		
12-19	1594	(16.9)
20-29	3207	(33.9)
30-39	1934	(20.5)
40-49	1062	(11.2)
50-59	823	(8.7)
60+	821	(8.7)
Sex		
Males	5987	(63.4)
Females	3454	(36.6)
Nationality		
Saudis	8554	(90.6)
Non-Saudis	887	(9.4)

From the Departments of Family and Community Medicine (Drs. Al-Shammari, Jarallah, Bamgboye), King Saud University and Primary Care Clinics (Dr. Olubuyide), King Khalid University Hospital, Riyadh.

Address reprint requests and correspondence to Dr. Al-Shammari: Associate Professor and Director of Primary Health Care Clinics, Department of Family and Community Medicine (34), College of Medicine, King Saud University, P.O. Box 2925, Riyadh 11461, Saudi Arabia.

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90.6% of the new patients. There was a male preponderance (1.73:1.00) overall and 71.3% of the patients were less than 40 years of age. The age distribution is also similar in both sexes and nationality. The frequency of the patients to the clinic was not related to the day, week or month of the study.

Table 2 shows the morbidity pattern among the patients according to the systems involved and in order of frequency. Ill-defined disorders, diseases of the skin, genitourinary, digestive, musculoskeletal and respiratory systems were the most frequent causes of morbidity, accounting for 70% of all new patients. The most common two diseases are analyzed in detail in Tables 3 and 4, respectively. Diseases of the genitourinary system were found in 1,049 patients. Of these, 21.7% were due to infections of the kidney, urolithiasis (19.8%), male infertility (13.9%), disorders of menstruation (13%) and others (31.6%). Nine hundred seventy-two patients had diseases of the digestive system. Acid peptic disease (50%) and other disorders of the intestine (12.8%) constitute the most commonly presenting diseases of this system. Of the 946 patients with diseases of the musculoskeletal system and connective tissue, 37.8% had nonspecific disorder of the back, 20.7% had osteoarthrosis, 10.4% had unspecified arthropathies, 10.4% had disorders of the muscle, ligament and fascia, and 20.7% had other diseases. Diseases of the respiratory system were found in 701 patients. Of these, 43.1% had acute upper respiratory infections, 22.5% had asthma, and 34.4% had other diseases. A full breakdown of all these diseases can be obtained from the correspondence author. While diseases of the skin and genitourinary system were 46.3% of the illnesses brought to the PCC by males, 51.2% of female patients presented mainly with ill-defined conditions and diseases of the respiratory and musculoskeletal systems.

TABLE 2. *The morbidity pattern of patients at the Primary Care Clinics of King Khalid University Hospital, Riyadh.*

Disease	ICD	Frequency	(%)*
Ill-defined illnesses	780-789	1893	(37.6)
Skin	680-709	1071	(31.1)
Genitourinary	580-629	1049	(43.7)
Digestive	520-579	972	(42.9)
Musculoskeletal	710-739	946	(35.7)
Respiratory	460-519	701	(29.5)
Injury	800-962	589	(27.7)
Infection	001-139	526	(31.0)
Metabolic	240-279	485	(31.8)
Circulatory	390-459	417	(23.0)
Others	-	792	(51.8)
Total	-	9441	(36.6)

ICD=International Classification of Diseases; *=the percentage of females is shown in brackets.

Table 5 shows the outcome of the management of the patient. Nearly two-thirds of the patients were treated at the PCC and the rest were referred to specialist clinics. Diseases of the skin and genitourinary systems formed the majority of those referred for specialist treatments. A low frequency of respiratory and ill-defined conditions were referred for such treatment.

Discussion

Within the well recognized limitations and incompleteness of hospital-based data, this analysis of the

TABLE 3. *Ill-defined illnesses of patients at the Primary Care Clinics of King Khalid University Hospital, Riyadh.*

Disease	ICD	Frequency	(%)
Abdominal symptoms	789	528	(27.9)
General symptoms	780	380	(20.0)
Symptoms involving nervous & musculoskeletal systems	781	248	(13.0)
Symptoms involving respiratory system & other chest symptoms	786	236	(12.4)
Others	-	505	(26.7)
Total	-	1897	(100)

ICD=International Classification of Diseases.

TABLE 4. *Diseases of the skin and subcutaneous tissue of patients at the Primary Care Clinics of King Khalid University Hospital, Riyadh.*

Disease	ICD	Frequency	(%)
Contact dermatitis & other eczema	692	192	(17.9)
Diseases of sebaceous glands	706	164	(15.3)
Other disorders of skin & subcutaneous tissue	709	158	(14.8)
Diseases of hair & hair follicles	704	109	(10.2)
Others	-	448	(41.8)
Total	-	1071	(100)

ICD=International Classification of Diseases.

TABLE 5. *The outcome of the management of patients at the Primary Care Clinics of King Khalid University Hospital, Riyadh.*

Disease	ICD	Patients referred for specialist treatment	(%)	Total No. of Patients seen
Ill-defined illnesses	780-789	106	(5.6)	1893
Skin	680-709	854	(79.7)	1071
Genitourinary	580-629	650	(70.0)	1049
Digestive	520-579	261	(26.9)	972
Musculoskeletal	710-739	170	(18.0)	946
Respiratory	460-519	63	(9.0)	701
Injury	800-962	100	(17.0)	589
Infection	001-139	113	(21.5)	526
Others	-	822	(57.4)	1432
Total	-	3139	(33.2)	9179

ICD=International Classification of Diseases.

morbidity pattern of patients at the PCC of our hospital may be considered to represent in broad outline the current pattern of diseases in a primary care setting in Saudi Arabia. We have shown that 70% of diseases at the PCC included common disorders such as ill-defined illnesses, diseases of the skin, genitourinary, digestive, musculoskeletal, and respiratory diseases. About 5% of the patients suffered from cardiovascular or metabolic disorders. This type of morbidity pattern is seen in almost all primary health care facilities in neighboring and developing countries such as Sudan and Pakistan.[3,4] That males are preponderant overall corroborates our previous observation from the analysis of adult admissions in this hospital and cannot be easily explained.[5] It may be because males have much greater freedom of movement in the Saudi society and can therefore attend clinics more frequently than the females. Similarly, that the majority of patients were below 40 years of age, the economically productive segment of society, is an indication of the demographic picture of Saudi Arabia as a young population.

Ill-defined conditions constituted 20% of all presentations. A vast majority of the illnesses are at such an early stage that definite diagnosis is not possible and the primary care physicians concerned were in no way constrained to establish a diagnosis in pathological terms. Of the ill-defined disorders, abdominal pain was the most common, constituting 28% of the cases. It is of interest to note that many patients in the Middle East channel their emotional difficulties through bodily symptoms. Recurrent or persistent pain for which no organic pathology is demonstrated is a fairly common phenomenon in this area.[6] The main difficulty of the physicians is to determine whether the abdominal pain is primary or secondary to emotional disorder or organic pathology.

Dermatological diseases constituting 11.3% of all diseases are less than the corresponding value found in the Westerners.[7] Eczema was the most common and was found in 17.9% of all the skin diseases. Basically, two factors cause eczema; allergic or sensitive skin and exposure to an allergen or an irritant. Climatic extremes in Saudi Arabia, such as heat and severe cold, and also psychological stresses, may promote the development of the skin lesion. Besides eczema, acne vulgaris was one of the most common dermatoses found in 15.3% of patients. This is higher than the incidence noted in Orientals.[8]

Genitourinary diseases formed 11.1% of all the diseases. Out of this, urinary tract infection mainly due to *Escherichia coli* formed 22% and showed a female preponderance as elsewhere.[9] Incidence of urolithiasis (20%) closely followed that of urinary tract infection. The relative incidence of the disorder has been suggested to be higher than the rest of the world.[10,11] Precipitating factors for urinary stone formation include production of concentrated urine due to excessive water loss from heat-induced sweating and hyperoxalluria from excessive tea consumption.[12] Other less common factors include urinary tract infection (urea-splitting organisms form an alkaline urine) and presence of foreign bodies such as bilharzia ova. To reduce the incidence of stone formation, it is therefore advisable that patients increase their fluid intake, especially during the hot summer months when the temperature may be maintained at 49°C. This should combat the water loss from sweating. It is also advisable that they should refrain from drinking too much tea and eating heavy meals rich in meat and oxalates.

Digestive diseases constituted 10.2% of all presentations and 49.1% of these were due to peptic acid disease as found in Westerners.[13] Smoking, an important environmental factor, and *H. pylori* are associated with peptic acid disease in Saudis.[14,15] There is, therefore, a need for greater awareness of smoking as an environmental hazard in the Kingdom, where cigarette smoking seems to be prevalent and relatively free from the restrictions that have been adopted in most developed countries.

Diseases of the musculoskeletal system constituted 10% of diseases of which back pain was the most common (37.8%). Most of this pain was due to musculo-ligamentous strain (70%), degenerative disc disease (25%), or facette arthritis (5%). Osteoarthrosis was the next most common, constituting 20.7% of musculoskeletal diseases. Osteoarthrosis of the knee showed a higher incidence of patellofemoral joint involvement compared to an investigation conducted in Sweden.[16] It is possible that the living habits (squatting and cross-leg sitting) are contributory mechanical factors to the common involvements of the knee joint in the Saudi population.

Respiratory tract diseases constituted only 7.4% of all diseases seen at the clinic. Upper respiratory tract infections (43%) were among the most frequent respiratory diseases, corroborating a previous report.[17] The primary care physician sees only a small fraction of patients with such problems, because most treat their symptoms at home with over-the-counter remedies or simply wait for the illness to heal by itself. To reduce the incidence of the disease, avoidance of overcrowding at home and schools, ensuring ventilation in homes, preventing smoke pollution and dust as well as improving personal hygiene among family members should be adopted.

Leishmaniasis, malaria, brucellosis, genetic blood disorders, and schistosomiasis are geographically spread within Saudi Arabia and the Middle East in general, though the relative incidence is low in our clinic.[18-22] Road traffic accidents, poisonings, or other emergencies did not feature in our series because such are usually treated at the Accident and Emergency Department of the hospital. On the other hand, 66% of all the cases seen at our clinic were of a minor nature and did not require referral for specialist treatment. Great care was exercised in deciding the appropriate involvement of other health care professionals. The most common cause for referral was skin diseases due to an easy access to dermatology care from our clinic.

It is conceivable that the commonly observed pattern of diseases in this study may change over a period of time, either due to the interventions adopted by the PCC or as part of social development or as a cumulative effect of both. The primary care physician not only has to be aware of such a change by periodically analyzing the available morbidity data but should also be trained to cope with this change in a regularly continuing medical education program of the primary health care. Moreover, the diagnostic and therapeutic facilities at the PCC should match any change in the morbidity pattern of the patients.

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OUTCOME OF SNAKEBITES IN AL BAHA DISTRICT

Fahed Al-Mohareb, FACP; Mohammed Al-Sadoon, PhD

Eighty-two patients with snakebites were seen at King Fahad Hospital (KFH) in Al Baha during the period from 1983G to 1989G and were retrospectively reviewed. Most common symptoms were pain (80.5%) and swelling (77%). Hemostatic abnormalities were found in 36 patients (44%) and were usually present on admission but may be delayed up to 20 hours after snakebite. All of these patients had local swellings, 17 had low hemoglobin and 29 had leukocytosis, suggesting systemic envenomation. Five patients had local skin necrosis, and three had to have fasciotomy for compartment syndrome. All patients, except one death, responded to treatment (antivenin, plasma products, or both). These data emphasize that hemostatic abnormality is the major complication of snakebite in the Al Baha District of Saudi Arabia. *Ann Saudi Med 1994;14(1):26-29.*

Al Baha is located in the Southwestern part of the Kingdom of Saudi Arabia which is in the Al Sarawat mountains about 2300 km above sea level.[1] King Fahad Hospital (KFH) is a 350-bed referral hospital catering to the needs of 300,000 people.[2] Snakebites are common in this region and almost all victims are seen at KFH. Fifty-one species have been identified in the Arabian peninsula.[3] These species belong to the families *Hydrophidae,* which is conventionally characterized as myotoxic; the *Elapidae,* which is neurotoxic; the *Viperidae,* which is vasculotoxic; the *Atractaspididae,* which has mixed characteristics in addition to the family *Colubridae* which include the mildly venomous back-fanged colubrids.[4] Nine species are known to be poisonous in inland Saudi Arabia, which include some representatives as *Naja haje arabicus, Walterinnesia aegyptia* (black desert cobra, yaim and al-sul); *Bitis arietans* (puff adder); *Echis carinatus, Echis coloratus* (Burton's carpet viper, Al-ragta); *Cerastes cerastes* (horned viper, Hayya umm jnaeb, Umm grun); and *Atractaspis micro-lepidota* (Abu shenf, Al Asuad).[3-5] Apart from a few case reports,[6-9] there are no published data on the epidemiology of snakebites or the clinical effects of envenomation in the Saudi population. This report summarizes the hematological abnormalities of snakebites, which are the most predominant complications in the Al Baha district.

Patients and Methods

All admissions with snakebites to KFH during the period from 1983G to 1989G were reviewed in a retrospective study. Clinical symptoms and signs, temporal relations between bite and hematologic abnormalities and complications were recorded. Serial clinical and laboratory parameters and treatments used were also recorded. Complete blood counting, liver and renal functions were done according to standard techniques using the Coulter counter and the automated bioanalyzer, respectively. Diaplastin (DIAMED AG) was used to measure prothrombin time (PT) and DiaCelin-L (DIAMED AG) for activated partial thromboplastin time (APTT). Fibrinogen kit (Instrumentation Laboratory Sud-Italy) was used for fibrinogen (Fg) and rapid latex test (Wellcome Diagnostica, England) for fibrinogen split products (FSPs). Some of the snakes responsible were brought by the victims, and those which were not brought could only be described.

Results

Eighty-two patients were identified with a history of snakebites by way of description of snakes or identification of snakes brought by the patient. There were 52 males and 30 females. Ages ranged from one to 75 years. The exact species was difficult to confirm. The most common symptoms were local pain present in 66 patients (80.5%) and swelling in 63 (77%). Fang marks were present in 48 (56%). Massive local swelling was present in 10 patients, generalized ecchymosis in two patients, bleeding from incision at bite area (done as first aid) in one patient and one patient had hematemesis.

Most patients were seen within one hour at local primary care centers, then transferred to KFH. Thirty-six patients received 20 cc or less of polyvalent antivenin (AV), (Pasteur anti *Bitis-Echis-Naja* venom serum) (AV), three received 30 cc, five received from 40 cc to 80 cc. From those with hemostatic abnormalities, 23 received AV at local primary care centers. Apparently those who felt initially well did not come until one to three days later

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From the Division of Hematology/Oncology, Department of Medicine (Dr. Al-Mohareb), King Khalid University Hospital and College of Science (Dr. Al-Sadoon), King Saud University, Riyadh.

Address reprint requests and correspondence to Dr. Al Mohareb: Department of Medicine (38), College of Medicine, King Khalid University Hospital, P.O. Box 2925, Riyadh 11461, Saudi Arabia.

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when they developed symptoms. Therefore, the number of patients reviewed may not reflect the actual number of snakebite victims.

PT, APTT and CBC were done on all patients. FSPs and fibrinogen were done on a few (Table). Hemostatic complications occurred in 36 patients (44%) (Table), 33 had prolonged prothrombin time (PT) and/or activated partial thromboplastin time (APTT). Seventeen of all patients had fibrinogen split products (FSPs) performed and 11 were elevated. Hemoglobin below 11 g/dl initially or while in the hospital was found in 17 out of the 36 patients with hemostatic changes. Thrombocytopenia (<150x10^9/L) was found in nine out of 17 patients.

Leukocytosis (>12x10^9/L) was present in 46 patients, 29 of whom had hemostatic changes. Hemostatic changes developed as early as one hour after the bite and in one patient, manifested only 20 hours later.

Five patients had local skin necrosis which required grafting; three had to have fasciotomy for compartment syndrome (two lower limbs and one upper limb). One patient, a five-year-old male, was brought in four hours after the bite and was comatose and in shock. He was intubated and mechanically ventilated but died a few hours later. This case could be attributed to *Atractaspis microlepidota* according to the description of the snake and previous reports.[7] His PT and APTT were markedly prolonged. He also received subcutaneous AV one hour after the bite at a local primary care center.

Only one patient had neurological complications; he had features of bulbar palsy developing six hours after the bite

TABLE: *Hematologic data of 36 patients with systemic envenomation.*

No.	Age (yrs)	WBC x10^9/L	Hgb g/dL	Plts x10^9/L	PT Secs	PTT Secs	FSPs µg/ml	Fg g/L
1	27	14.4	09.2	145	16.1	36.7	>160	0.3
2	75	11.0	06.8	091	25	50	>160	0.25
3	60	35.7	08.5	026	16.4	65.7	>140	ND
4	03	53.3	06.6	023	24.3	>120	>80	ND
5	18	18.6	11.8	016	12.4	25.9	>320	ND
6	03	64.7	06.7	020	16.5	55.2	>80	ND
7	09	20.5	07.9	020	23.5	48.6	<20	ND
8	60	17.2	07.6	076	>90	>120	ND	ND
9	04	22.5	11.7	118	14.4	45.8	ND	ND
10	33	15.3	10.1	072	16.5	41	ND	ND
11	17	08.9	08.0	144	>90	>120	ND	ND
12	14	09.5	06.6	146	15.7	26.4	ND	ND
13	60	19.7	14.3	069	12.4	24	ND	ND
14	12	16.9	06.6	080	>90	>120	ND	ND
15	12	13.5	10.7	083	>90	>120	ND	ND
16	07	13.7	10.2	052	>90	>120	ND	ND
17	05	48.8	09.4	059	>90	>120	Died	ND
18	07	18.5	13.6	319	13.2	23.5	>80	ND
19	16	14.2	14.4	281	>90	>120	>80	ND
20	04	17.7	09.6	404	16.8	49.7	>80	ND
21	50	21.0	13.7	201	>90	>120	>80	ND
22	14	11.5	11.5	300	>90	>120	>80	ND
23	10	10	14	N	15.0	38.8	ND	ND
24	10	14.9	12.1	318	>90	>120	ND	ND
25	05	17.7	09.2	197	15.0	56.0	ND	ND
26	22	05.8	15.3	171	>90	>120	ND	ND
27	40	11.5	10.4	220	18.2	40.2	ND	ND
28	04	16.8	11.7	N	17.5	41.7	ND	ND
29	25	28	17.9	302	14.5	37.5	ND	ND
30	46	15.2	15.5	260	>90	>120	ND	ND
31	06	15.9	10.9	N	>90	34.5	ND	ND
32	42	13.6	12.3	175	>90	>120	ND	ND
33	70	23.4	13.6	168	>90	45.6	ND	ND
34	11	13.2	13.2	302	>90	>120	ND	ND
35	10	39.6	12.6	357	18.5	38.4	ND	ND
36	18	15.8	12.0	273	23.5	37.1	ND	ND
RR					11-14	26-36	<10	2-4

N=normal; ND=not done; RR=reference range; WBC=white blood cell (count); Hgb=hemoglobin; Plts=platelets; PT=prothrombin time; PTT=partial thromboplastin time; FSPs=fibrin split products; Fg=fibrinogen.

and improved 1-1/2 hours after AV infusion. These neurological complications, in addition to the description of the snake, attribute the responsibility to the cobra snake *Naja haje arabicus*.

Treatments given were as follows: 27 received AV alone, 15 received AV and fresh frozen plasma (FFP), two received FFP and cryoprecipitate, one received cryoprecipitate alone.

One patient developed lethargy after AV infusion and was treated with corticosteroid and improved. Almost all patients received booster doses of tetanus toxoid as well as antitoxin.

Discussion

Snake venoms are complex mixtures of proteins, many with enzymatic activity.[10-12] The exact composition is variable and may include coagulant and fibrinolytic, proteolytic, and neurotoxic proteins. Hemostatic manifestations are one of the serious complications. These hemostatic abnormalities are complex but some follow certain patterns: 1) Afibrinogenemia without thrombocytopenia,[11-14] characterized by fibrinogen levels as low as 0, elevated FSPs without clot formation and mild decrease in factors II, V, VII, VIII, and X as well as plasminogen. Thrombocytopenia was not noted. *In vitro* studies demonstrated a purely thrombin-like activity.[11] In this study, there were 18 patients with prolonged PT and APTT and normal platelets, four with elevated FSPs. Although coagulation factors were not done, the symptoms were similar to the reported findings. 2) Afibrinogenemia and thrombocytopenia,[15-17] characterized by nonclotting blood, prolonged PT and APTT, very low fibrinogen, elevated FSPs, and profound thrombocytopenia $<50 \times 10^9$/L in most patients. The activities of factors II-XII were normal. This was determined to be the result of the thrombin-like action of the venom on fibrinogen; and 3) snake venom which activates prothrombin; this was found to be the result of the venom with properties distinctly different from Factor Xa (the venom of *Echis carinatus*.)[18,19] Reports of *Echis carinatus* bite were consistent with disseminated intravascular coagulation (DIC) with prolonged PT, APTT, profound thrombocytopenia and intravascular hemolysis. *In vitro* studies showed that the venom activates prothrombin and aggregates platelets and was inhibited by heparin. However, other reports of *Echis carinatus* bites surprisingly stress the rarity of associated thrombocytopenia.[6,20]

Fifteen of our patients had prolonged PT, APTT and low platelets. FSPs were done in six and were elevated. Fourteen had low hemoglobin. Of these 14, seven had serial bilirubin and/or plasma hemoglobin (performed within 24 hours) and were not elevated in six, which is against hemolysis and suggests that DIC is not a common manifestation, contradicting the reported cases about *Echis carinatus*, which is one of the known poisonous snakes in Saudi Arabia.[4,5]

Anemia due to viper bites is not common and depends on the amount of lost erythrocytes externally from oozing blood vessels and internally into the local exudate of the bitten limb, behind the peritoneum, etc., and so hemolytic activity is rarely important clinically except possibly as a factor in renal failure.[8,10] Most patients who had low hemoglobin had a markedly swollen limb, which is characteristic of viper bite poisoning which affects vascular and lymphatic permeability and results in exudation either of plasma or of whole blood.[10]

Three of our patients had to have fasciotomy for compartment syndrome for this complication.

Collapse with unrecordable blood pressure can occur within a few minutes and is thought to be secondary to activation of the kinin system (this usually resolves spontaneously within 30 to 60 minutes), whereas shock which develops later is a main cause of death in viper bites,[21] probably secondary to hypovolemia, but shock may develop before the limb becomes grossly swollen. Other causes of shock include pulmonary thrombus, pulmonary edema, and cardiac effects. Only one patient was brought in with shock and he had generalized purpura and a completely blue left foot. He died despite aggressive life support measures. This patient had received AV one hour after the bite, which could point to the possibility of anaphylaxis to the AV. The possibility of an anaphylactoid response to venom would not be excluded as a correlation of this situation and previous reports.[22]

This review is also in agreement with the fact that swelling associated with *Viperidae* bites usually indicates systemic envenomation, as all of the patients with hemostatic complications had swellings and all other patients had no swellings.[10] Three patients had no complications. We would also like to stress the necessity to observe patients with snakebite for at least 24 hours, as one of our patients manifested hemostasis 20 hours later.

This review emphasizes that hemostatic abnormalities are the major complication of snakebites in the Al Baha district. Species such as *Atractaspis microlepidota, Naja haje arabicus, Bitis arietans, Echis carinatus, Echis coloratus,* and *Cerastes cerastes,*[4] which are found in the district, may be responsible for most of the casualties. It was unfortunate that most of the patients did not have all the hemostatic parameters performed and we were not able to identify the types of snakes. Using the ELISA method for detection of venom in serum or urine should be helpful in identifying the types of snakes responsible in the future.[23]

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MULTIPLE BRAIN ABSCESSES AT KING KHALID UNIVERSITY HOSPITAL

Abdulhakim Jamjoom, FRCS, Ed(SN); Zain Alabedeen Jamjoom, MD; Abdulrahman Shameena, MD;
Saleh Al-Hedaithy, PhD; Abdulrahman Tahan, MRCP(UK); Naim-Ur-Rahman, FRCS Ed(SN)

The authors reviewed six cases of multiple brain abscesses that were treated at King Khalid University Hospital (KKUH) over an eight year period. This represented 22% of the total brain abscesses treated during the same period. The series is unusual in that the infective pathogens were fungi *(Fonsecaea pedrosoi)* in two patients (33%) and an aerobic actinomycete *(Nocardia asteroides)* in one patient (16%). Two patients treated elsewhere with antibiotics empirically for one month died at three and 28 days following admission. The poor outcome was probably related to the delay in obtaining a microbiological diagnosis and commencing the appropriate antimicrobial therapy. The importance of early identification of the pathogen in patients with multiple brain abscesses is stressed. *Ann Saudi Med 1994;14(1):30-32.*

There are a few reports which present an overall account of brain abscess in Saudi Arabia;[1-3] however, reports on the clinical characteristics of patients with multiple brain abscesses in this region is lacking. This article is a review of six cases of multiple brain abscesses that were treated in a single neurosurgical unit in Riyadh, Saudi Arabia over an eight year period. It is appreciated that the number of cases reported in our study is small; however, this is not surprising considering that multiple brain abscesses remain a relatively rare disease that has been documented in the international literature either by case reports or small series ranging from seven to 34 cases.[4-10] It is hoped that the presentation of our cases will heighten the awareness of clinicians about this pathology, which should always be considered in the differential diagnosis of multiple intracranial space-occupying lesions (SOL). In addition, the aim of the paper is to emphasize the importance of early microbiological diagnosis in these patients who still face the risks of a considerable mortality rate.

Case Histories: Out of a series of 27 consecutive patients with brain abscess that were treated at King Khalid University Hospital (KKUH) between 1984G and 1992G, there were only six cases in which the abscesses were multiple. These were four males and two females with an age range from 10 to 72 years (mean 39 years). Four patients were Saudis and two were non-Saudis (one Indonesian and one Yemeni). None of the patients had any obvious evidence of immunosuppression. The HIV status, serum immunoglobulins and the cell mediated immunity response were assessed for the last three patients (Cases 4-6) and were found normal. The duration of symptoms ranged from two to eight weeks (median 4.5 weeks). On admission to the neurosurgical unit, all patients had clinical features of increased intracranial pressure and focal neurological deficits. Their Glasgow Coma Score (GCS) on admission ranged from six to 14 (median eight to 10). Only two patients were febrile (Cases 2 and 4) and three patients had convulsions (Cases 1,3,6). Blood cultures were performed on admission for all patients and were found negative in all cases. The primary source of infection was not detectable in four cases, while the

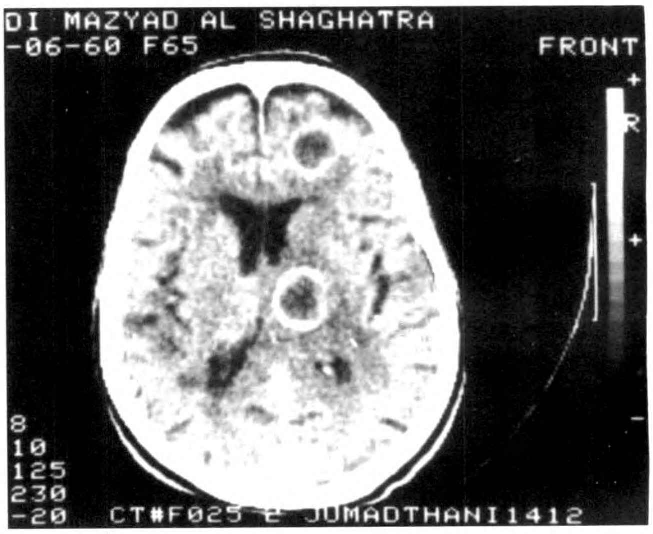

FIGURE 1. CT of brain with IV contrast shows right frontal and thalamic abscesses with moderate edema (Case 5).

From the Divisions of Neurosurgery (Drs. A. Jamjoom, Z. Jamjoom, Ur-Rahman), Neurology (Drs. Shameena, Tahan), and Department of Microbiology (Dr. Al-Hedaithy), King Khalid University Hospital, Riyadh.

Address reprint requests and correspondence to Dr. A. Jamjoom: Assistant Professor and Consultant Neurosurgeon, Division of Neurosurgery, Department of Surgery, King Khalid University Hospital, P.O. Box 7805, Riyadh 11472, Saudi Arabia.

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TABLE: *The clinical characteristics of cases in the series.*

	Appearance on CT Scan					
Case	Number of Abscesses	Site	Surgery	Organism	Antimicrobial Therapy	Outcome
1	8	Both hemispheres	None	Meningococcus (CSF)	Penicillin, Chloramphenicol, Metronidazole	Good*
2	2	Bifrontal	BHA+ (2 lesions)	*Fonsecaea pedrosoi*	Amphotericin, flucytosine	Died
3	3 & empyema	Right frontal/parietal	Craniotomy Evac Empyema asp. 2 abscess	*Staphylococcus aureus*	Vancomycin, Flucloxacillin, Metronidazole	Good
4	2	Right frontal	BHA (1 lesion)	*Staphylococcus aureus*	Vancomycin, Flucloxacillin, Metronidazole	Good
5	2	Right frontal & thalamic (Fig.1)	BHA (1 lesion)	*Fonsecaea pedrosoi*	Amphotericin, flucytosine, Fluconazole	Good
6	>10	Both hemispheres (Fig. 2)	BHA (1 lesion)	*Nocardia asteroides*	Ceftriaxone, Flucloxacillin, Metronidazole	Died

BHA+=Bur hole aspiration; Good*=return to normality.

infection was postmeningitis in one case (Case 1) and post-traumatic in another case (Case 3). The other clinical characteristics of the cases in the series are summarized in the Table (Figures 1 and 2).

Three patients (Cases 2,5,6) had been admitted elsewhere for a period of three to five weeks before arrival to our unit. They were treated empirically with multiple antimicrobial agents. Cases 5 and 6 were treated with antituberculous drugs as possible cases of multiple tuberculomas, while Case 2 was treated empirically with antibiotics as a possible case of bacterial abscesses. Case 6 arrived on our unit comatose with numerous abscesses all over the brain and extensive edema (Figure 2); and she died three days later. Her infection was found to be caused by an aerobic actinomycete *(Nocardia asteroides)*. Case 2 was an elderly male with bifrontal abscesses caused by fungi *(Fonsecaea pedrosoi)*. He died four weeks after admission despite aggressive surgical and antimycotic therapy. Case 5 was found to have two abscesses also caused by *Fonsecaea pedrosoi* (Figure 1). She did well despite the delay in starting antifungal treatment. At follow-up ranging from one to six years (mean 3.5 years), the four surviving patients (Cases 1,3-5) have all returned to normality except for one patient (Case 3) who remains epileptic.

Discussion

With the widespread availability of the computed tomography (CT) scan, multiple brain abscesses are being detected more frequently. Recent reports suggest a two to three-fold increase in the incidence of multiple abscesses since the advent of computed tomography.[10] Twenty-two percent of all our brain abscesses were multiple. This is slightly higher than most reports, which quote a range of 4% to 20% for the incidence of multiple abscesses in brain abscess series.[5,7-9,11] There is, however, one report which stated that up to 35% of brain abscesses may be multiple.[6]

The mortality rate in our small series was 33%, which is slightly higher than the 0% to 30% reported as the mortality rate for multiple brain abscesses in series in the post CT scan era.[5-7] There was a delay in the referral to the neurosurgical unit of the two cases that died. Their empirical medical treatment was found to be inappropriate and ineffective as the culture of the aspirated pus proved the infective agents to be *Fonsecaea pedrosoi* (Case 2) and *Nocardia asteroides* (Case 6). As a result of the delay in aspirating the abscesses and starting the appropriate antimicrobial treatment, both patients arrived at our unit with a depressed consciousness level (GCS 6) and the CT scans of both patients demonstrated enlargement of the abscesses. It is recognized that the outcome of patients with brain abscess is influenced by delays in the diagnosis,[5,7,11,12] depression of consciousness level on admission,[5,7,8,11,12] inappropriate or inadequate doses of antibiotics,[7,12] ineffective surgery,[13] progressive enlargement of the abscess despite initial treatment,[6,14,15] the size of the abscess,[14] depth of the abscess from the surface, whether cortical or deep,[6,15] ignorance of the primary source of infection[7,8] and the length of history.[8]

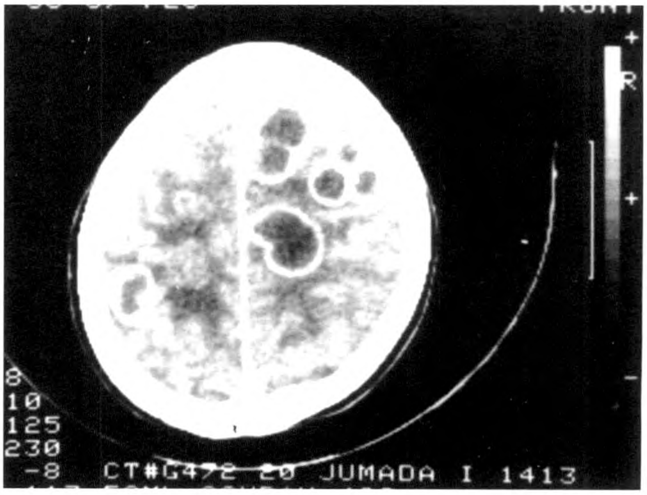

FIGURE 2. CT of brain with IV contrast shows multiple abscesses all over both hemispheres with severe edema (Case 6).

It is appreciated that this series is too small to present any general information regarding multiple brain abscesses in Riyadh, Saudi Arabia. The unusual feature of our patients, however, was the finding that the primary source of infection was unknown in 66% of cases; a primary otogenic, dental or sinus infection did not cause the abscesses in any of our cases. Streptococci, which are recognized to be the most common pathogen in single and multiple brain abscesses,[5,7] were not cultured in any of the cases. The finding of a fungal pathogen in two patients and an aerobic actinomycete in one patient in this series is also unusual when compared to previous reports.[5-8,11]

It is reported that the type of surgery does not influence the outcome of patients with multiple brain abscesses.[6,7,10] Since it is difficult to extirpate a multifocal infection with surgery, it is generally accepted that the place of surgery in patients with multiple brain abscesses is in the role of a diagnostic rather than a therapeutic procedure, unless one particular abscess assumed a very large size, causing increased intracranial pressure. Five of our patients had bur hole aspiration of one or two of the most accessible lesions. For small and deeply located lesions, good results have been reported with stereotactic aspiration[6] but this was not necessary in any of our patients.

There have been reports of success in treating multiple abscesses with antibiotics alone.[14] In such circumstances, the choice of antimicrobial therapy is based on the cultured pathogen from blood or from the primary source of sepsis. Our Case 1 made a good recovery after treating the postmeningitic multiple brain abscesses with antibiotics without any aspiration. However, in the absence of a cultured pathogen from the blood or from the primary source of infection, the situation is more obscure. Empirical treatment not only necessitates prescribing a large number of antimicrobial agents with their potential side effects, but they are unlikely to cover rare pathogens such as fungi and actinomyces which accounted for 50% of our small series. Therefore, along the same line as that reported by Bouchama et al,[16] who stated the value of biopsy in the diagnosis of intracranial tuberculoma, the authors stress the importance of early microbiological diagnosis obtained by aspirating one or more of the abscesses, either by free hand or stereotactically, so that the most effective antimicrobial agents may be started with no delays.

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LAPAROSCOPIC CHOLECYSTECTOMY: THE FIRST YEAR EXPERIENCE

Adnan Bakr Mofti, FRCS, FRCS(Glas); Nader Mohamad Hussein, FRCS(Ed), CABS;
Suleiman Ibrahim Suleiman, FRCS; Saif Ahmed Ismail, MD; Gyan Chand Jain FRCS(Ed),
Abdulhameed Abdulhadi Al-Momen FRCSI, FICS

A total of 307 consecutive patients with symptomatic gallstones were admitted for cholecystectomy. Two hundred seventy patients (88%) were considered suitable for laparoscopic cholecystectomy. Forty-two of these (17%) were admitted on an emergency basis. The procedure was accomplished successfully in 246 patients (91%), while in the remaining 24 patients (9%), the attempt had to be abandoned and converted to open cholecystectomy. Postoperative complications, mostly minor, occurred in 22 patients (9%). Suspected common bile duct stones were treated with endoscopic retrograde cholangiopancreatography (ERCP) prior to surgery. The mean operative time was 82 minutes and 70% of the patients were discharged home within 48 hours after surgery and more than 90% were sent home by the third postoperative day. The results suggest that laparoscopic cholecystectomy is feasible for the majority of patients with symptomatic gallstones. *Ann Saudi Med 1994;14(1):33-36.*

The introduction of laparoscopic cholecystectomy by Mouret in 1987G probably represents the most significant changes in general surgical technique this century.

Since the advent of this exciting and important development in the field of general surgery, several reports from the USA and Europe have demonstrated that laparoscopic cholecystectomy is safe and attended by less postoperative pain and disability than the conventional open procedure. Moreover, it allows earlier discharge from the hospital and a more rapid return to work and usual activities.[1-7]

Since we have the privilege of being the first government hospital to introduce this procedure in Riyadh, Saudi Arabia, we report our first year of experience using laparoscopic cholecystectomy.

Patients and Methods

The first laparoscopic cholecystectomy procedure was carried out at Security Forces Hospital (SFH) in October 1991G. All patients with gallstones have been offered the laparoscopic procedure when considered appropriate. Over a period of 12 months, (October 1991G to October 1992G), a total of 307 consecutive patients with symptomatic gallstones were considered for cholecystectomy under the supervision of three consultant general surgeons. All patients, unless contraindicated or appearing unfeasible from the start, were offered laparoscopic removal of the gallbladder. Preoperative endoscopic retrograde cholangiopancreatography (ERCP) was performed when there was a history of jaundice, pancreatitis, abnormal liver function tests or abdominal ultrasonography showing dilatation of the common bile duct >8 mm.

Operative Technique

This is mainly based on that developed by Reddick and Olsen,[8] but with some modifications. All patients received a single dose of intravenous second generation cephalosporin with the premedications. Antibiotic treatment was continued or changed as indicated. Subcutaneous heparin was administered when indicated. All patients underwent the procedure under general anesthesia with endotracheal intubation and routine use of a nasogastric tube, which is removed before extubation at the conclusion of the surgery. Urinary bladder catheterization was not performed in any patient.

A 2 cm long transverse skin incision is made supraumbilically (occasionally infraumbilically). The linea alba is then incised and the peritoneum is opened under direct vision. A pursestring suture is then applied to the linea alba and tightened after introduction of a disposable 10 mm surgiport cannula. Pneumoperitoneum is established by using CO_2 via the surgiport through an electronic rapid flow insufflator set to maintain the pneumoperitoneum at a pressure of 13 mm/Hg. A 10 mm 0° diagnostic laparoscope attached to a video camera is then introduced through this umbilical surgiport cannula to visualize the intraperitoneal contents. Illumination is provided by a xenon light source with automatic intensity

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From the Department of Surgery, Security Forces Hospital, Riyadh.
Address reprint requests and correspondence to Dr. Mofti: P.O. Box 3738, Riyadh 11481, Saudi Arabia.
Accepted for publication 24 April 1993.

control. The video camera is connected to two high resolution television monitors located so as to allow all members of the surgical team to visualize the procedure clearly. The patient is then placed in a 30 to 40 degree reverse Trendelenburg position and the operating table is rotated to the left for 20 to 30 degrees. This position will allow the abdominal viscera to fall away from the gallbladder.

All subsequent accessory trocars are placed under direct laparoscopic visualization and guidance. A 10 mm surgiport trocar and cannula are placed in the epigastric region two fingerbreadths below the xiphoid and just to the right of the midline. Two 5 mm surgiport trocars and cannulae are then introduced, one two fingerbreadths below the right costal margin in the midclavicular line and the other lower down in the anterior axillary line. These accessory ports are used for insertion of various laparoscopic instruments to hold, manipulate and dissect the gallbladder.

The later 5 mm port is utilized for a ratcheted grasping forcep which grasps the gallbladder fundus and retracts it cephalad. The midclavicular 5 mm port is utilized for insertion of a grasping forcep to hold the gallbladder neck and is best controlled and manipulated by the surgeon's left hand.

The 10 mm epigastric port is utilized for various laparoscopic instrumentation used to dissect, cauterize, cut, ligate, etc., the anatomic structures as required. This will allow clear delineation of Calot's triangle and after clear exposure of the cystic duct and artery, an endo clip applicator is introduced through the 10 mm epigastric port and titanium clips are applied proximally and distally to both the cystic artery and the cystic duct. The artery and the duct are then transected by laparoscopic serrated scissors. Occasionally, when the cystic duct is wide, an endo loop suture is used to reinforce the ligation of the cystic duct stump. Operative cholangiogram can be performed before applying the distal endo clip on the cystic duct (operative cholangiography was performed on three cases only).

The gallbladder is then removed from its bed using electrocautery through the hook coagulator or Semm hook coagulator scissors. Prior to complete detachment of the gallbladder, the liver bed is checked for possible sites of bleeding or bile leak. Saline irrigation and aspiration of the operative field may be carried out at this stage as required. We do not routinely drain our endo cholecystectomy sites. However, if a drain is required, we use a small closed suction drainage catheter usually inserted through one of the 5 mm surgiport sites and secured to the skin. The laparoscope is then transferred to the epigastric port while a heavy claw grasping forcep is introduced through the umbilical port to grasp the gallbladder at its neck, and under direct laparoscopic visualization, the gallbladder is partially pulled into the cannula and the entire surgiport cannula and gallbladder are then withdrawn from the abdomen together after dividing loose the pursestring suture. Very occasionally, we enlarge the opening in the linea alba as required to allow delivery of a distended gallbladder with large stones.

Subsequently, all surgiports are removed, the CO_2 is expressed and the operating table is readjusted to the normal horizontal position. Only the periumbilical fascial defect is closed with continuous 0 Vicryl suture and skin incisions are closed with auto clips.

All laparoscopic equipment and endo instruments are from Solos Endoscopy, Inc., USA, while all disposable surgiport trocars and cannulae, endo clip applicators and endo loop sutures are from Auto Suture International, Inc., USA.

Postoperatively, patients are usually allowed oral fluids four to six hours after recovery and full breakfast the following morning. Postoperative pain control is achieved by a single dose of intramuscular pethidine and thereafter by oral analgesics or nonsteroidal anti-inflammatory drugs.

Results

Over the period of study, from October 1991G to October 1992G, 307 patients were admitted to the general surgical unit at SFH with symptomatic gallstone disease. Thirty-seven patients (12%) were considered, for various reasons, unsuitable for laparoscopic cholecystectomy

TABLE 1. *Patients considered unsuitable for laparoscopic cholecystectomy procedure (37 pts).*

No. of Patients	(%)	Remarks
12	32%	Positive HBsAg
8	22%	Acute cholecystitis with palpable RHC mass ± jaundice
7	18%	Unavailability of the system
4	11%	CBD stones, failed or unavailable, ERCP
4	11%	Previous upper abdominal surgery ± ventral hernia
1	3%	Acute fulminating pancreatitis
1	3%	Cardiopulmonary insufficiency

HBsAg=hepatitis B surface antigen; CBD=common bile duct; ERCP=endoscopic retrograde cholangiopancreatography.

TABLE 2. *Distribution of patients and sex.*

No. of Patients	M (%)	F (%)
307 patients with symptomatic gallstones	50 (16%)	257 (84%)
37 patients considered unsuitable for laparoscopic cholecystectomy	10 (20%)	27 (11%)
Laparoscopic cholecystectomy attempted on 270 patients (88%)	40 (80%)	230 (89%)
Successfully completed laparoscopic cholecystectomy procedure on 246 patients (91%)	33 (83%)	213 (93%)
Laparoscopic cholecystectomy converted to open procedure on 24 patients (9%)	7 (17%)	17 (7%)

M=males; F=females.

(Table 1). Hence, laparoscopic cholecystectomy was attempted on the remaining 270 patients (88%) who form the core of this report.

Laparoscopic cholecystectomy procedure was successfully completed on 246 patients, while in the remaining 24 patients, the procedure had to be abandoned and converted to the classical open cholecystectomy procedure. This gives a conversion rate of <9% in this series.

Table 2 shows the overall distribution and sex of the patients, while Table 3 lists the various reasons for which we had to convert laparoscopic procedures to the classical open cholecystectomy procedures. The main reasons were inflammatory adhesions and unfavorable anatomy.

Among the 246 successfully accomplished laparoscopic cholecystectomy procedures, 42 patients (17%) were admitted on an emergency basis. Of these, 23 patients had acute cholecystitis, nine patients had persistent biliary colic, seven patients had acute pancreatitis and three patients had mucocele or empyema of the gallbladder. Preoperative ERCP was performed on 38 patients and postoperative ERCP on two. One patient developed mild acute pancreatitis after preoperative ERCP. Intraoperative cholangiography was attempted on three patients and was successful in only two. In all three patients, there were no filling defects in the ducts. Closed suction drainage was used in 18 patients (7%). Almost all drains were removed within the first 30 hours postoperatively and in the majority of those patients, the drainage was not significant. The median operating time was 78 (range 45 to 145) minutes.

Intraoperative difficulties and pitfalls were encountered in 47 patients. These were dealt with accordingly without undue morbidity or mortality. Table 4 shows these difficulties and actions taken.

There were no deaths in this series but postoperative complication, although mostly minor, occurred in 22 patients (9%). In no patient did we encounter intra-abdominal sepsis, wound infection or viscus perforation. Common bile duct injury occurred in only one patient (0.4%) and this later required a formal surgical repair. Almost 70% of our patients were discharged home within the first 48 hours after surgery and only < 5% were required to stay in the hospital for more than five days.

Discussion

Our results during the first year demonstrate clearly the several advantages and safety of the laparoscopic cholecystectomy procedure, especially when we consider the "learning curve" effect and our policy of considering "all comers", which reflects favorably the superiority of the laparoscopic procedure over other conventional and nonconventional methods known for management of gallstones. Although we considered all patients, whether present urgently or electively, we were partially selective in excluding a group of patients as shown in Table 1. One might argue that the majority of our excluded patients could have been suitable candidates. This is partially true after the availability of resources and expertise. After we acquired a second laparoscopy system and instrument set, exclusion due to unavailability or failure of the system decreased to almost nil. Recently, we acquired a third system and instrument set that are allocated for hepatitis antigen-positive patients.

TABLE 3. *Reasons for conversion to open cholecystectomy in 270 attempted laparoscopic procedures.*

Reasons	No. of Patients	% Rate
Inflammatory dense and extensive adhesions	14	5%
Difficult unfavorable anatomy	7	2.6%
Uncontrolled bleeding via laparoscopy	2	0.7%
Significant bile leakage	1	0.4%
Total	24	< 9%

TABLE 4. *Intraoperative pitfalls and actions encountered in 246 patients.*

Pitfalls	No.	Actions
Gallbladder perforation	30 (12%)	Saline lavage and aspiration (26 patients)
Bile spillage only	21	Closed suction drainage (11 patients)
Bile and stone spillage	9	Antibiotic treatment (16 patients)
Controllable bleeding	17 (7%)	Saline lavage and aspiration (11 patients)
From cystic artery injury	5	Suturing (2 patients)
From gallbladder bed	10	Electrocautery
From omental adhesion	2	Closed suction drainage (6 patients)
		Blood transfusion (1 patient)

Laparoscopic exploration of the bile duct, although technically difficult, is safe and effective.[9,10] However, we have no experience in such technique and we rely on selective preoperative ERCP to deal with suspected bile duct stones. ERCP was attempted preoperatively on 40 patients and postoperatively on two. Common bile duct stones were found in only 12 patients (30%) and were successfully removed by basket extraction and/or sphincterotomy in 10 patients before laparoscopic cholecystectomy was attempted.

Although our conversion rate (9%) may be considered relatively high, analysis of the data shows that it is much lower (<4%) if we consider the elective cases only. Nevertheless, the reasons necessitating conversion are mostly potentially avoidable. Our complication rate compares favorably with other published reports.[5,6,11] Apart from the one case of common bile duct (CBD) injury, we encountered no other major complications. This shall favor greatly the laparoscopic procedure over the conventional open cholecystectomy.

We found the introduction of the periumbilical laparoscope cannula by open method quite safe and effective and allowed us to remove the gallbladder from the abdomen without the need to aspirate the bile or crush the stones. Although later development of a periumbilical hernia is a potential possibility, we did not encounter any and will be watching for such on a long-term follow-up basis.

The mean operative time of 78 minutes compares favorably with most reported series.[6,8,12,13]

Seventy percent of the patients returned home within 48 hours of the procedure and more than 90% were home by the third postoperative day. Although the vast majority of our patients were females, almost all were able to resume their home activity comfortably within the first postoperative week. Meanwhile, the male patients, mostly military personnel, were able to resume their work and duties within two weeks postoperatively.

In conclusion, we found laparoscopic cholecystectomy quite safe, minimally invasive, and associated with an acceptable rate of morbidity as long as the operating team has obtained the necessary expertise. The procedure is quite feasible for the urgently and electively presented patients.

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ROLE OF FUNCTIONAL CAST BRACING IN THE TREATMENT OF COLLES' FRACTURE

Gulzar Ahmad Hagroo, MS(Orth); Tejinder Singh Sethi, MS(Orth)

This work presents the results of 100 consecutive cases of Colles' fracture treated by functional cast bracing in supination as advised by Sarmiento and colleagues, using locally made metallic hinge, followed up for 18 weeks. The results have been compared with those obtained by other authors using functional cast bracing and also other conventional conservative methods including percutaneous pinning. There is a wide variation in the results obtained by various authors using different techniques, but on the whole, our results with functional cast bracing in supination have been among the best in any published series. *Ann Saudi Med 1994;14(1):37-41.*

In the management of Colles' fracture, the technique of immobilization, extent of the plaster, and the position of the hand and the forearm in plaster have been the points of controversy for decades among orthopedic surgeons. Some surgeons immobilize with the wrist in flexion in a below-the-elbow cast,[1-3] while others have used extreme pronation and right angle flexion and ulnar deviation of the wrist in the treatment of this fracture, i.e., cotton-loder position.[4,5] Some surgeons have used above-the-elbow cast with the forearm fully pronated in an attempt to prevent recurrence of supination deformity.[6,7] Many advocate immobilization with the forearm in supination.[8-10] The value of early mobilization in the treatment of Colles' fracture has been emphasized by several surgeons[3,4,8,10] although some of the investigators have used functional cast bracing in supination with encouraging results.[8-10] On the contrary, in 1984G, Stewart et al, in a comparative study, found no anatomical or functional advantage with functional cast bracing over conventional casts.[11] Functional cast bracing permits freedom of motion of all joints during the reparative process, thus reducing the sequelae of prolonged immobilization. The brachioradialis muscle (a powerful elbow flexor with the forearm in neutral or pronation and the only muscle attached to the distal radial fragment) becomes a deforming force in pronation and is probably the main reason for the common and rapid recurrence of original deformity; on the other hand, in supination the brachioradialis loses its strength and the biceps becomes the main flexor of the elbow.[12]

To find the efficacy of functional cast bracing in supination in the treatment of Colles' fracture, we evaluated the results of this type of treatment using locally made metallic hinge and compared these with those of conventional methods of treatment.

Material and Methods

This study was conducted on 100 consecutive patients with Colles' fracture following fresh trauma, who attended the Governmental Hospital for Bone and Joint Surgery, Srinagar Kashmir, India from October 1985G to January 1987G. Patients with bilateral Colles' fracture, generalized joint disease, and with associated injury of any other part of the body were excluded from the study. Patients were assessed clinically and radiologically. Radial deviation, radial length and volar tilt were measured on standard anteroposterior (AP) and lateral (L) views and compared with the normal side with the help of lines shown in Figure 1. A reference line was drawn in conjunction with central longitudinal axis of the radius in both AP and L radiographs. Then two perpendicular lines to the central line and one line through the ulnar and radial margins of the radial articular surface were drawn on AP view. The perpendicular distance between the first two lines measured in millimeters (mm) was the radial length. The angle formed by the third line with the first perpendicular line was radial deviation in degrees. Measurement of volar-dorsal tilt was done by drawing a perpendicular line to the center line of the radius on lateral view and a line through the volar and dorsal margins of the distal radial articular surface. The angle between these two lines was recorded as zero degree if the radial articular surface was parallel to the perpendicular line: a +ve angle if the articular surface showed a volar tilt, and a -ve angle if there was a dorsal tilt.

Fractures were divided into two groups: undisplaced -- fractures with radial shortening of 1 to 5 mm, loss of some volar tilt and up to 5° of dorsal tilt and loss of radial

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From the Department of Orthopedics, Bone and Joint Surgery Hospital Barzalla, Government Medical College, Srinagar Kashmir, India.
Address reprint requests and correspondence to Dr. Hagroo: P.O. Box 56773, Riyadh 11564, Saudi Arabia.
Accepted for publication 27 April 1993.

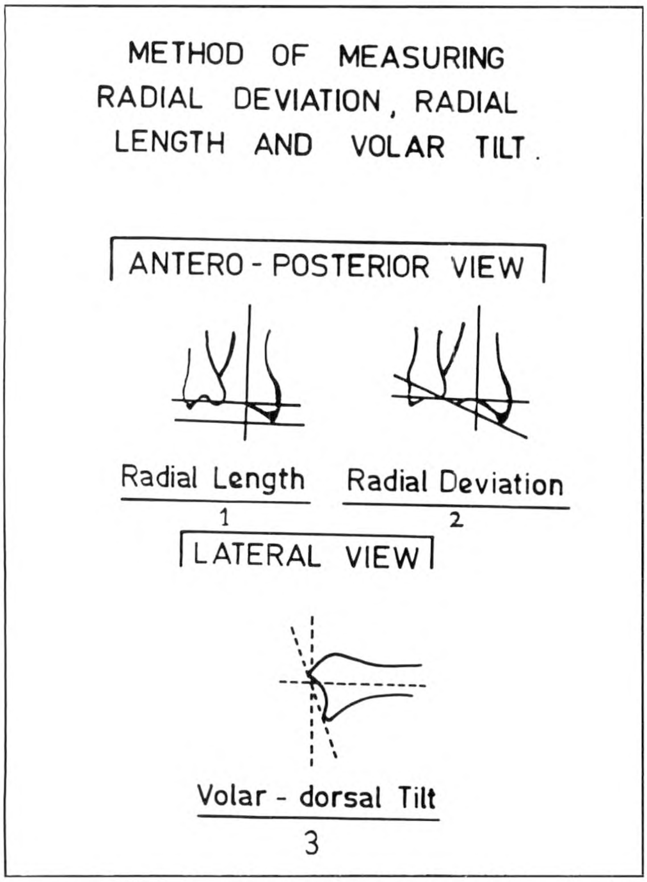

FIGURE 1. Method of radiological measurements.

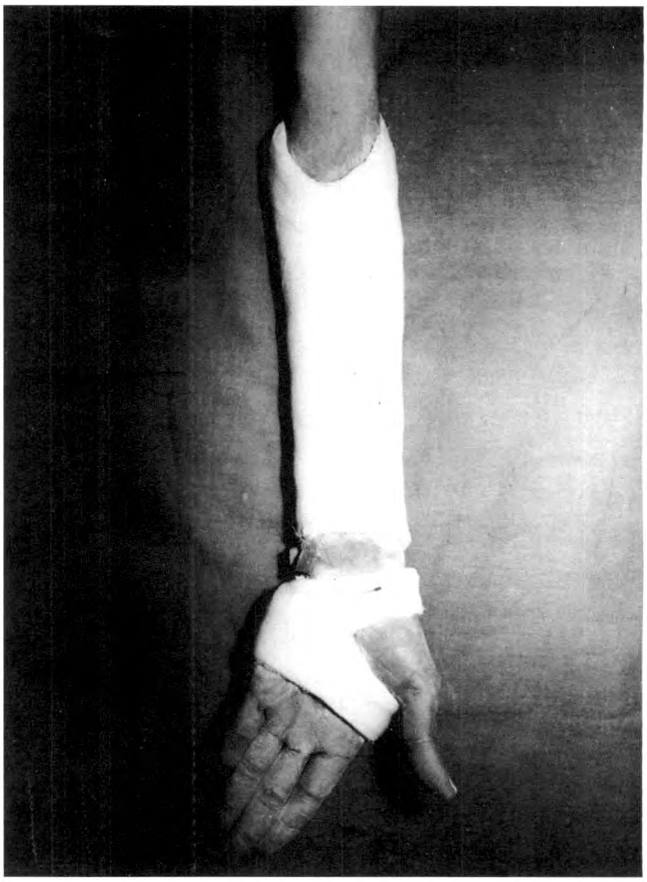

FIGURE 2. Front view of the cast brace with the forearm in supination and the wrist in ulnar deviation.

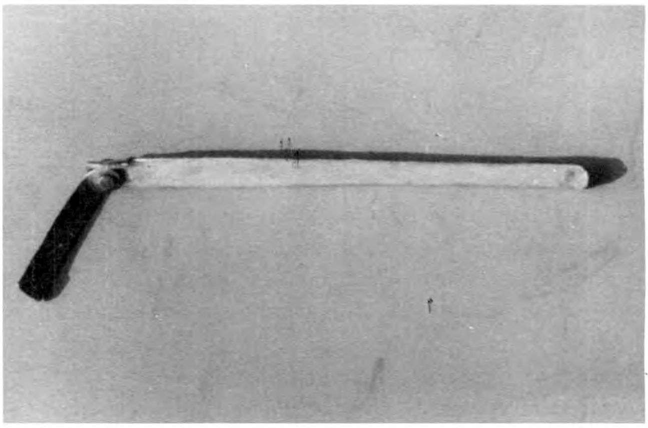

FIGURE 3. Metallic hinge, left side.

deviation of 1° to 5°; displaced -- fractures with radial shortening of more than 5 mm, dorsal tilt of more than 5° and loss of radial deviation of more than 5°. Undisplaced fractures were immobilized directly in a cast brace under intravenous sedation. Displaced fractures were first treated with closed reduction under general anesthesia and then a two-piece above-the-elbow cast brace applied with the elbow in some flexion and the wrist in volar flexion and ulnar deviation. The proximal part was applied with the forearm in supination from the elbow to the wrist with supracondylar extension on the posterior, lateral and medial side of the elbow which limited pronation and did not allow full extension of the elbow. A distal piece of the plaster was applied around the hand proximal to the metacarpophalangeal joints up to the base of the hand excluding the thumb (Figure 2). The wrist was hinged with the help of a locally made metallic joint, separate for the right and left side (Figure 3), placed on the ulnar side of the wrist and its two limbs were incorporated in a two-piece plaster. This hinge allowed movements at the wrist from the neutral position to full palmar flexion, but no dorsiflexion (Figure 4). After cast brace, radiographic measurements were repeated, and the patients were advised to move the shoulder, wrist, and fingers gradually as and when tolerated. The patients were assessed clinically for any pain, swelling, stiffness of the fingers or shoulder at two weeks and after removal of the cast brace at six weeks. Clinical measurements of ranges of motion by goniometer and radiographic measurements were done at six weeks and recorded. Finally at the end of 18 weeks, results were evaluated using criteria laid down by Lidstrom in 1959G for anatomical results[13] and criteria of Gartland and Werley in 1951G for functional results.[5]

TABLE 1. *Summary of observations.*

No. of	Age (yrs)		Sex		Side involved		Mode of injury*		Type of fracture	
Patients	Range	Mean	M	F	Right	Left	Direct	Indirect	Undisplaced	Displaced
100	20-71	38.14 ±SD 11.29	34	66	50	50	4	96	26	74

*=direct included road traffic accidents and direct hit on the wrist; indirect included fall on the outstretched hand; ±SD=standard deviation.

TABLE 2. *Changes in radiological profile of the injured wrist between prereduction and postreduction position (after cast brace application).*

	No	Loss			Gain		
	change	1-5	6-10	11 or >	2-4	5-7	8 or >
Radial deviation* (degrees)	16	10	-	-	18	40	16
Radial length (mm)	15	11	-	-	20	38	16
Volar tilt (degrees)	18	8	-	-	22	34	18

*=radial deviation indicates deviation of the distal fragment of the radius in relation to its own longitudinal axis and not the direction of deviation.

TABLE 3. *Changes in radiological profile from postreduction position up to six weeks (within cast brace).*

	No	Loss			Gain		
	change	1-5	6-10	11 or >	2-4	5-7	8 or >
Radial deviation* (degrees)	23	42	5	-	27	3	-
Radial length (mm)	23	40	7	-	27	3	-
Volar tilt (degrees)	23	41	6	-	28	2	-

*=radial deviation indicates deviation of the distal fragment of the radius in relation to its own longitudinal axis and not the direction of deviation.

Observations

Out of 100 Colles' fractures, 74 were displaced and 26 undisplaced. Age and sex distribution and clinical profile are shown in Table 1. Alteration in radial deviation, radial length and volar tilt due to displacement, tilt or rotation of the distal radial fragment was evaluated in terms of loss or gain as compared to normal. No gain was observed in any patient. However, 74 displaced fractures had loss of all the three parameters. In 26 undisplaced fractures, eight cases had 1° to 5° shift in radial deviation from normal, 1 to 5 mm of radial shortening in 10 cases and alteration of 1° to 5° of volar tilt in six cases. Changes in the radiological profile between prereduction and postreduction position and within the cast brace are detailed in Tables 2 and 3, respectively. Loss of 1° to 5° was observed in radial deviation and volar tilt in 10 and eight patients, respectively, belonging to the undisplaced group, while 11 patients showed shortening in radial length after application of the cast brace; on the other hand, in all 74 displaced fractures, gain in all radiological parameters was noted (postreduction). One of the most important findings observed in 74 patients with displaced fractures was that of loss of radial deviation, radial length and volar tilt in as many as 47 cases in one way or another, and on the contrary, 30 cases did show some gain in all these parameters at the end of six weeks (Table 3). Twenty-three undisplaced fractures had Grade I anatomical and excellent functional results. The correlation between anatomical and functional results of the rest of the patients is detailed in Table 4. Clinical follow-up of the patients is shown in Table 5. All the ranges of motion of the injured wrist began increasing appreciably from two weeks onward and reached to almost normal at the end of 18 weeks. Eighty-eight patients had satisfactory (Grade I and II) and 12 patients had unsatisfactory (Grade III) anatomical end results. No patient had Grade IV end result. Functional

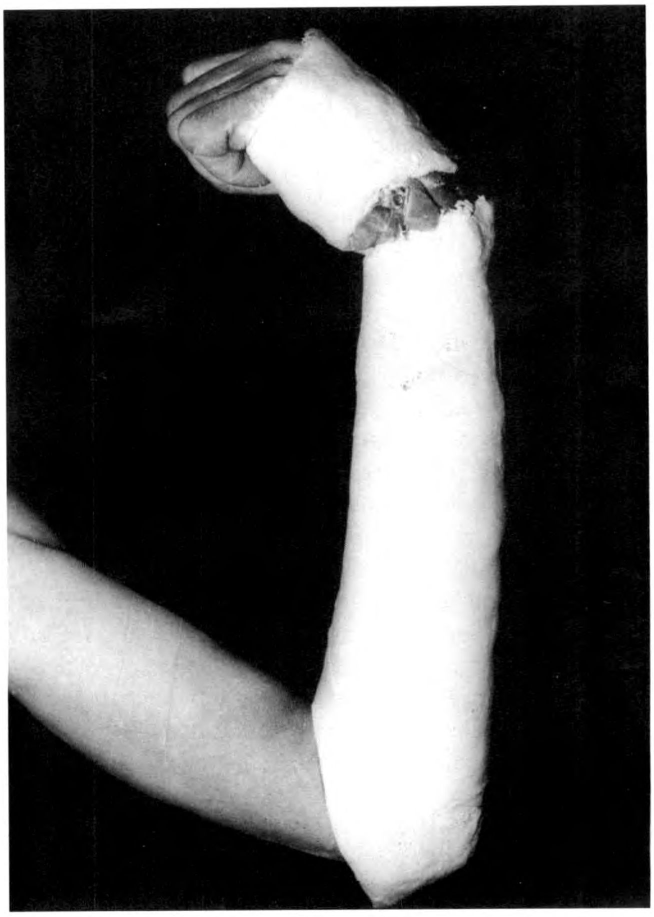

FIGURE 4. Side view of the cast brace that allows flexion and extension of the elbow, palmar flexion of the wrist, and dorsiflexion to neutral.

TABLE 4. *Correlation of loss or gain in radial deviation, radial length, and volar tilt in cast brace and result.*

		Results							
		Anatomical Grades				Functional			
	No. of Patients	I	II	III	IV	Excellent	Good	Fair	Poor
No change	23	23	-	-	-	23	-	-	-
Loss*	47	-	35	12	-	-	39	8	-
Gain*	30	30	-	-	-	26	4	-	-
Total	100	53	35	12	-	49	43	8	-

*=radial deviation and volar tilt are in degrees and radial length in millimeters.

TABLE 5. *Clinical follow-up of cases.*

	2 weeks	6 weeks	18 weeks
Pain	80	-	-
Swelling of			
Thumb	76	-	-
Fingers	32	-	-
Stiffness of fingers	23	16	-
Tenderness*	x	29	3
Stiffness of shoulder	16	13	2

*=tenderness on ulnar side of the wrist; x=could not be elicited due to presence of cast brace.

assessment at 18 weeks showed that out of 53 patients with Grade I anatomical results, 49 had excellent and four had good functional results while 35 patients with Grade II anatomical results all had good functional results. Of the 12 patients with Grade III anatomical results, four had good and eight had fair functional results. None had poor functional results (Table 4).

Discussion

Significant morbidity is a common feature of Colles' fracture due to redisplacement of the distal fragment in casts during the four to six week healing period. This has been termed as "chronic instability" of Colles' fracture.[14] This process is not affected either by method of treatment or early mobilization of the wrist and hand. A malunited fracture produces a deformed, stiff, weak and painful wrist, jeopardizing the rehabilitation process of the injured limb.[3] Functional cast bracing in supination is directed to reduce these complications and therefore, offers patients a speedy return to the routine activities of life.

The age incidence in this series does not concur with those of Sarmiento et al or Van der Linden and Ericson, who reported an age range of 15 to 92 years (mean 49 years) and 16 to 92 years, respectively in their studies.[9,15] The higher incidence of Colles' fracture among the younger age group in our series (mean 38.14) could probably be attributed to heavy snowfall that the Kashmir valley experienced during the winter months of 1985G to 1986G. This was followed by severe cold, freezing of snow and even lakes, which forced elderly people to stay in their homes during these months. However, the younger people were not restrained much from their normal activities, so they fell victim to Colles' fracture.

Eighty percent of our patients complained of varying degrees of pain in the wrist during the first two weeks of treatment. Early mobilization of the injured wrist is expected to evoke more pain and render such treatment unacceptable by the patient. In our opinion, this can be avoided with proper reassurance of the patient; that is, with the progression of the healing process, pain will gradually decrease. Moreover, with his/her active participation in the treatment, early mobilization is likely to yield encouraging results. The advantage of early mobilization of the injured part is that the blood flow to the bone and soft tissues is quickly restored to normal and joint stiffness is prevented.[3] In the present study, 16 patients experienced mild stiffness of the fingers after removal of the cast brace. This problem had been influenced by distal slipping of the cast brace, preventing full flexion of metacarpophalangeal joints. Thirteen patients had stiffness of the shoulder at six weeks. All of these patients were elderly women and most of them improved with physiotherapy. After removal of the cast brace, there was tenderness on the ulnar side of the wrist on forced pronation and supination in 29 patients who had associated fracture of the ulnar styloid process. This could be because of injury to triangular fibrocartilage followed by adhesions, fibrosis and shortening of the attachment between it and the ulna. As a result, triangular fibrocartilage can no longer glide freely to and fro on the head of the ulna due to supination and pronation.[16] Twenty-six of these patients improved after local infiltration with 2% xylocaine (2 ml) and 40 mg of triamcinolone (1 ml).

In our series, 35% of the patients had prominence of the ulnar styloid plus radial deviation of the hand while 12% had dorsal deformity (dinner fork). In 1976, Hollingworth reported prominence of the distal end of the ulna in 53.8% of cases. Functional assessment of these showed that only 85.2% had satisfactory results.[6] On the other hand, Perkins warranted that a Colles' fracture, however skillfully treated, may leave behind a deformed wrist.[2] There were 92% satisfactory (excellent and good) and 8% unsatisfactory (fair and poor) functional results in our series, although it is very difficult to compare the results of the present series with other reported data because of variation in the type of fracture, type and period of immobilization, period of follow-up and criteria of evaluation. However, the results

TABLE 6. *Comparison of different types of treatment.*

Author	Ref	Year	Method of treatment	No. of patients	Results	
					Satisfactory	Unsatisfactory
Gartland & Werley	[5]	1951	CR + BEPS	60	68%	32%
Depalma	[17]	1952	CR + UP + BEC	60	68%	32%
Mason	[1]	1953	CR + BEC	100	95%	5%
Green & Gay	[4]	1956	CR + AEC	75	83%	17%
Older et al	[18]	1965	CR + PF + BEC	100	90%	10%
Sarmiento et al	[8]	1975	CR + FCB	41	82%	18%
Gupta & Aggarwal	[10]	1981	CR + FCB	21	95%	5%
Present series			CR + FCB	100	92%	8%

CR=closed reduction; BEPS=below elbow plaster splint; UP=ulnar pinning; PF=pin fixation; BEC=below elbow cast; AEC=above elbow cast; FCB=functional cast bracing.

are compared in Table 6.[1,4,5,8,10,17,18] Unsatisfactory functional results in the present series could probably be attributed to loss of reduction in a cast brace and poor patient compliance.

In conclusion, functional cast bracing in supination effectively maintains the reduction of the Colles' fracture, while at the same time allowing motion at the wrist. It therefore allows early and complete return to normal function. By eliminating the influence of the brachioradialis muscle, which acts as a deforming force in Colles' fracture, functional cast bracing in supination reduces the incidence of residual deformity. Functional cast bracing for this common fracture does not need special resources or expertise, because it is cost efficient and can be applied at any orthopedic center.

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TREATMENT OF CYCLOPHOSPHAMIDE-INDUCED INTRACTABLE HEMORRHAGIC CYSTITIS

M. Shouki Bazarbashi, MD; Muhammad S. Shurafa, MD; Chatchada Karanes, MD

We report the successful use of prostaglandin F_2 alpha continuous bladder irrigation in two patients for the treatment of intractable cyclophosphamide-induced hemorrhagic cystitis which was resistant to conventional therapy in two patients. A 0.7 mg% solution of prostaglandin F_2 alpha was used for continuous bladder irrigation at a rate of 150 to 200 cc/hr for four days. The response was complete in both patients and no side effects were noted. *Ann Saudi Med 1994;14(1):42-44.*

Hemorrhagic cystitis is one of the more challenging problems in urology practice. This can be secondary to infections, chemotherapy, or radiation therapy.

Prostaglandins have recently been reported to be an effective treatment for hemorrhagic cystitis.[1] They are usually given by an intravesical instillation for a few hours daily over several days. Most of our patients with hemorrhagic cystitis did not tolerate this method of administration due to the development of severe bladder spasms, leakage of the drug around the Foley catheter as well as the development of intravesical clots that prevented contact of the medication with the bladder wall.

In the following two cases, we report the use of prostaglandins for the treatment of cyclophosphamide-induced hemorrhagic cystitis. This was administered as a continuous bladder irrigation through a three-way Foley catheter and we observed successful results in both cases with this form of treatment.

Case 1: A 56-year-old male with multiple myeloma was treated with cyclophosphamide 600 mg/m^2 daily for four days monthly starting June 1987G after documentation of resistant disease. The patient was subsequently hospitalized in September 1988G with massive hematuria. An evaluation showed no evidence of infection, stones or tumor involvement. Continuous bladder irrigation with sterile isotonic saline failed to stop the bleeding. Cystoscopy and bladder biopsy, after two weeks of conservative management, demonstrated diffuse hemorrhagic cystitis secondary to cyclophosphamide. Bladder irrigation with formalin and alum was attempted without improvement. Having successfully treated a patient with the same condition with prostaglandin F_2 alpha (PGF_2) intravesical instillation,[1] we attempted the same therapy, but without success because of severe bladder spasms and leakage around the Foley catheter. A cystostomy was performed thereafter to remove a large clot obstructing both ureters and ligation of both internal iliac arteries was performed without success. Several days later, we decided to give PGF_2 by continuous bladder irrigation as a 0.7% solution. Twenty-four hours after starting the bladder irrigation, the urine was completely clear without any visible blood. The irrigation was continued for four days and there was no recurrence of the hematuria. The patient was then discharged and continued to be free of hematuria until he expired from progression of his disease.

Case 2: A 38-year-old male with non-Hodgkin lymphoma was admitted for allogeneic bone marrow transplantation (BMT) in July 1990G because of disease progression in the retroperitoneum. The cytoreductive regimen consisted of intravenous cyclophosphamide 1.8 gm/M^2/day, etoposide 400 mg/M^2/day for four days and carmustine (BCNU) 600 mg/M^2 on the fifth day followed by bone marrow infusion from a human lymphocytic antigen (HLA) identical brother. Due to a history of cyclophosphamide-induced hemorrhagic cystitis, Mesna (2-mercaptoethanesulfonate) was also given during the cyclophosphamide administration. Three days after completion of chemotherapy, the patient developed massive hematuria. Cystoscopy to remove large clots and cauterization of bleeding sites was performed. Severe hematuria and bladder spasm continued in spite of continuous isotonic saline irrigation of the bladder and recovery of the platelet count above 100,000 by day 20 post BMT. After an unsuccessful attempt at intravesical retention of 0.7 mg% of PGF_2 due to severe bladder spasms, we began continuous bladder irrigation with 0.7

From the Department of Oncology (Dr. Bazarbashi), King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia. Division of Hematology (Dr. Shurafa), Henry Ford Hospital, Detroit; Division of Hematology/Oncology (Dr. Karanes), Wayne State University, Detroit, Michigan, USA.

Address reprint requests and correspondence to Dr. Bazarbashi: Department of Oncology (MBC-64), King Faisal Specialist Hospital and Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia.

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mg% PGF_2 for four days. The hematuria decreased significantly by the second day and the urine became clear at the end of four days. Except for a brief period of mild hematuria six weeks later, he has been free of bladder symptoms and is currently in remission.

Discussion

Cyclophosphamide chemotherapy can be complicated by hemorrhagic cystitis, the etiology of which is thought to be mediated by the action of certain metabolites, predominantly acrolein, on the urothelium.[2] The incidence is variable and may be as high as 40%.[3] It can occur with high-dose[4] or with continuous low-dose therapy,[5] and can range from mild microscopic hematuria to severe and life-threatening forms.[6] Prevention of cyclophosphamide-induced hemorrhagic cystitis is often more effective than treatment once it has developed. This includes careful attention to the total cyclophosphamide dose, adequate hydration of the patient during and following the administration of cyclophosphamide and particularly encouraging results seen with the prophylactic administration of sodium 2-mercaptoethanesulphonate (Mesna).[7,14]

Various forms of treatment of cyclophosphamide-induced hemorrhagic cystitis have been suggested, none of which are very effective and some are associated with significant toxicity. Such treatments include measures as simple as hydration, bladder irrigation with isotonic saline, or intravesical instillation of silver nitrate,[8] alum,[9] formalin,[10] and phenol.[11] In the more intractable cases, cystoscopy with fulguration, amino caproic acid, vasopressin, bilateral epigastric or internal iliac artery ligations or embolization and cystostomy with urinary diversions or cystectomy[6,12,13] have been tried with variable successes. Often these measures are ineffective or not without significant adverse effects.

Recently, hemorrhagic cystitis secondary to cyclophosphamide has been shown to be ameliorated by the daily instillation and retention of 200 cc of 0.7 mg% solution of PGE_2 or PGF_2 alpha in the bladder for four hours.[1,15] However, this form of therapy is limited by the ability of the patient to tolerate the clamping of the Foley catheter for four hours and by the reduced capacity of the urinary bladder in this condition. The presence of severe bleeding, as in our patients, may result in the formation of large clots, which limit the accessibility of the bladder mucosa to the irrigating solution, reducing its effectiveness. Also, technically it may not be possible to maintain the irrigating solution in the bladder due to leakage around the catheter. In an attempt to overcome all these difficulties, we used continuous bladder irrigation with the PGF_2 solution, which resulted in rapid cessation of bleeding. The treatment was continued for a total of four days to prevent recurrence and ensure the success of the treatment.

The mechanism by which prostaglandins act in treating hemorrhagic cystitis is not well known. It is possible that they exert this effect via a cytoprotective action on the bladder mucosa similar to their role on the gastric mucosa.[15] This concept is supported by the finding that the symptoms of schistosomal bladder ulcers improve with local prostaglandin instillation.[16] The cytoprotective effect on the bladder mucosa is thought to be secondary to increasing the intracellular cyclic adenosine monophosphate level, which in turn increases local glycosaminoglycan production, which inhibits the contact and adherence of chemicals to the urothelium.[17,18] We noted no systemic or local side effects from the local prostaglandin bladder treatment although flushing, nausea and vomiting are known side effects of parenterally administered PGF_2.

The successful result we report should encourage using continuous PGF_2 bladder irrigation early in the course of cyclophosphamide-induced hemorrhagic cystitis. Although this form of treatment is expensive, costs may be defrayed by the savings made from reducing the hospital stay and decreased need for surgical intervention. Further clinical trials are needed before advocating this therapy as standard treatment for this condition.

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Review Article

FINE NEEDLE ASPIRATION BIOPSY DIAGNOSIS OF RENAL MASSES IN CHILDREN: A BRIEF REVIEW

Mohammed Akhtar, MD, FCAP; Fouad Al-Dayel, MD,
M. Ashraf Ali, MD, FRCPC, FCAP

A variety of benign and malignant neoplasms may involve the kidneys in infants and children. The most common of these is Wilms' tumor (WT); however, other neoplasms such as clear cell sarcoma (CCS), malignant rhabdoid tumor (MRT), congenital mesoblastic nephroma (CMN), cystic nephroma (CN), cystic partially differentiated nephroma (CPDN), and renal carcinoma (RC) may also be seen.[1-5] All these lesions may have identical clinical presentation. Preoperative diagnosis of these tumors may help to reduce the number of diagnostic tests and procedures resulting in prompt therapy and a shortened stay in the hospital. This may be particularly useful for those treatment protocols that use preoperative chemotherapy for renal malignancies.[6] Furthermore, in a patient whose tumor is relatively advanced and therefore unsuitable for surgical resection, fine needle aspiration biopsy (FNAB) diagnosis may help in initiating proper chemotherapy or radiation therapy in order to reduce the tumor size, thus rendering it amenable to surgical resection.[7]

Several recent studies have shown that FNAB may be an extremely useful technique for diagnosing renal neoplasms.[8-17] However, definitive FNAB diagnosis of these tumors requires a thorough knowledge of the various histologic patterns encountered in these tumors and a clear understanding of corresponding histologic and cytologic correlations. In this review, morphologic features of renal masses in infants and children as seen in aspiration smears are briefly outlined and pertinent histologic correlations are emphasized. This is based on our experience over many years with FNAB diagnosis of these tumors and also on the relevant studies published in the literature.

Wilms' Tumor

Wilms' tumor is the most common malignant neoplasm of the kidney in children. The morphology of this tumor is quite complex with a range of morphologic patterns that closely mimic stages of embryogenesis of the kidney.[3,18] Thus, similar to the developing kidney, Wilms' tumor is composed of three morphologic components that are intermixed in variable proportions. These include blastemal, epithelial, and stromal components. In addition, there may be heterologous cellular elements that may be epithelial or (more commonly) mesenchymal. Consequently, FNAB appearance of these neoplasms is also quite variable. In most of the WT, blastemal components appear to be predominant, although epithelial and tubular differentiation may also be encountered frequently. Rarely, a WT is virtually completely composed of mesenchymal elements. The blastemal pattern is

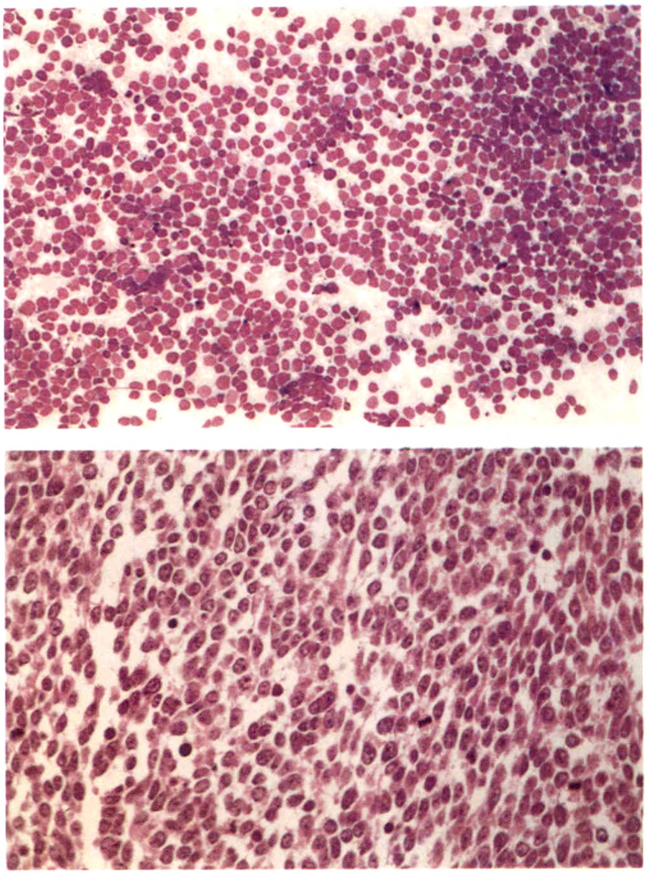

FIGURE 1. (A) Aspiration smear showing blastemal pattern in WT. The cells are randomly arranged and are undifferentiated. Diff-Quik stain 100x. (B) Histologic section showing blastemal pattern in a WT. Hematoxylin and eosin stain 100x.

From the Department of Pathology and Laboratory Medicine, King Faisal Specialist Hospital and Research Centre, Riyadh.

Address reprint requests and correspondence to Dr. Akhtar: Department of Pathology (MBC 10), King Faisal Specialist Hospital and Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia.

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represented in the FNAB smears as loosely arranged sheets of small, relatively uniform undifferentiated cells (Figures 1A and 1B).[8,9] In some areas, these cells may form small clusters. Earliest evidence of epithelial differentiation in FNAB smears is the presence of variable numbers of slightly larger pale staining cells separated from one another by smaller undifferentiated blastemal cells (Figures 2A and 2B). As the differentiation progresses further, these epithelial cells tend to be arranged in small round clusters forming primitive tubules in which variable numbers of small blastemal cells may still be recognized (Figures 3A and 3B). In more well differentiated tubules, only epithelial cells are present and usually a lumen can also be recognized in the aspiration smears. Stromal differentiation is usually recognized when spindle-shape cells along with slightly mucoid background are present (Figures 4A and 4B). Rhabdomyosarcomatous differentiation within the stroma may be recognized by the presence of large polygonal to irregularly shaped cells, relatively abundant light blue cytoplasm with one or more nuclei (Figures 5A and 5B). Cartilaginous, lipomatous, and other mesenchymal elements may also be encountered occasionally (Figures 6A and 6B).

An important feature of Wilms' tumor that has a significant impact on prognosis is the presence of anaplasia.[2] This may be diffuse or focal. FNAB diagnosis of dysplasia is possible on the basis of the criteria identical to those used in histologic examination. These are increased cell size, hyperchromasia, and atypical mitosis. In view of the limited cellular sample obtained by the FNAB, it is unlikely that focal anaplasia would be diagnosed by this technique. However, the chances of detection of anaplasia by FNAB would increase considerably when it is present diffusely through the mass.[8]

Clear Cell Sarcoma

Clear cell sarcoma is the second most common malignant neoplasm of the kidney in pediatric patients.[1,2] In the National Wilms' Tumor Study, it was initially designated as a sarcomatous variant of Wilms' tumor. It had also been reported earlier as a bone metastasizing sarcoma of the kidney. Subsequently, the term clear cell sarcoma of the kidney (CCSK) was used in recognition of the fact that this tumor is histogenically distinct from Wilms' tumor. Several excellent studies describing the histologic features of this neoplasm have been published in the literature.[13,19-21] A large number of overlapping histologic patterns has been recognized. Clear cell pattern is the most common. Other less frequent patterns include epithelioid, trabecular, or neurilemoma-like pattern, fibrosis and stromal hyalinization, cystic pattern, and angiectatic pattern. In the clear cell pattern, the tumor cells are loosely arranged and are separated by a delicate interlacing network of fibrovascular septa containing an arborizing network of small blood vessels. The cells are relatively small with uniform nuclei and a small amount of clear cytoplasm (Figure 6A). FNAB diagnosis of CCSK is primarily dependent upon recognition of a clear cell pattern since it is the dominant component in most of the neoplasms. The cytologic features of the remaining, less common, patterns have not yet been clearly understood. FNAB smears from CCSK consist of loosely arranged round stellate or spindle-shape cells with round to ovoid uniform nuclei, some of which may show longitudinal grooves.[13,14] These cells are arranged randomly in a background of mucoid intercellular material that stains light pink to deep purple in the Diff-Quik stained smears (Figure 6B). None of the features seen in smears from Wilms' tumor are encountered.

Malignant Rhabdoid Tumor

Malignant rhabdoid tumor of the kidney (MRTK) was characterized by Beckwith and Palmer in 1978 as a highly aggressive variant of Wilms' tumor but was later recognized as a separate entity with unknown histogenesis.[2,22,23] These neoplasms are composed

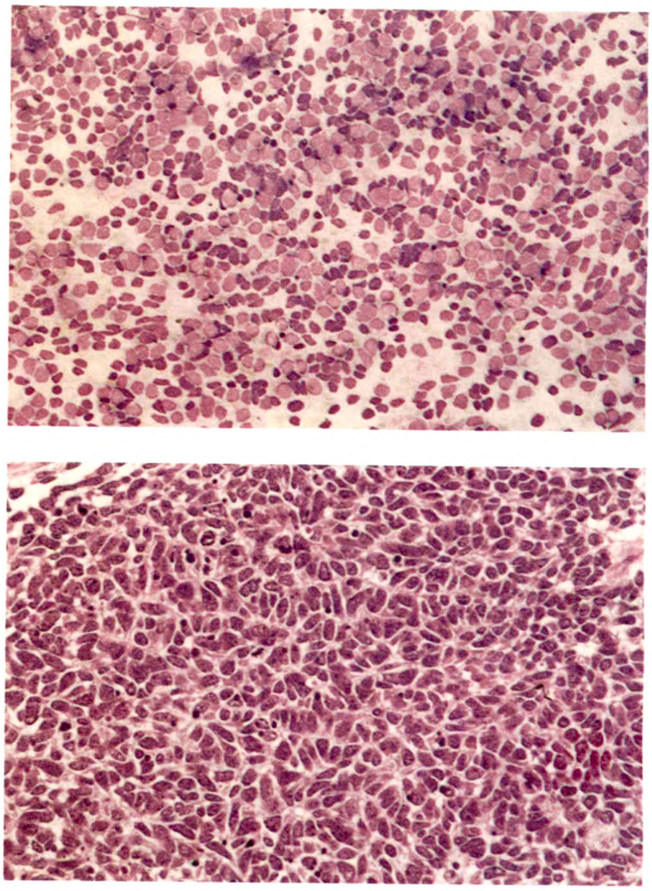

FIGURE 2. (A) Another aspiration smear from WT showing epithelial differentiation in a background of blastemal cells. Diff-Quik stain 100x. (B) Histologic section for WT featuring blastemal pattern with early epithelial differentiation. Hematoxylin and eosin stain 100x.

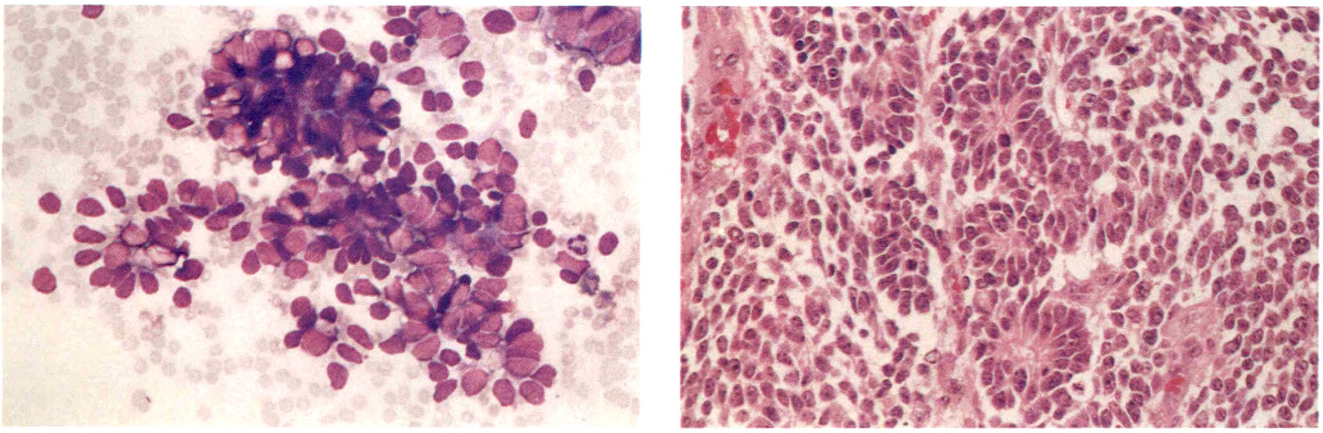

FIGURE 3. (A) A cluster of primitive tubules in an aspiration smear from WT. The tubules are composed of relatively large pale cells intervening small cells with dense nuclei. Diff-Quik stain 150x. (B) Photomicrograph showing WT with blastemal pattern and tubular differentiation. Hematoxylin and eosin stain 150x.

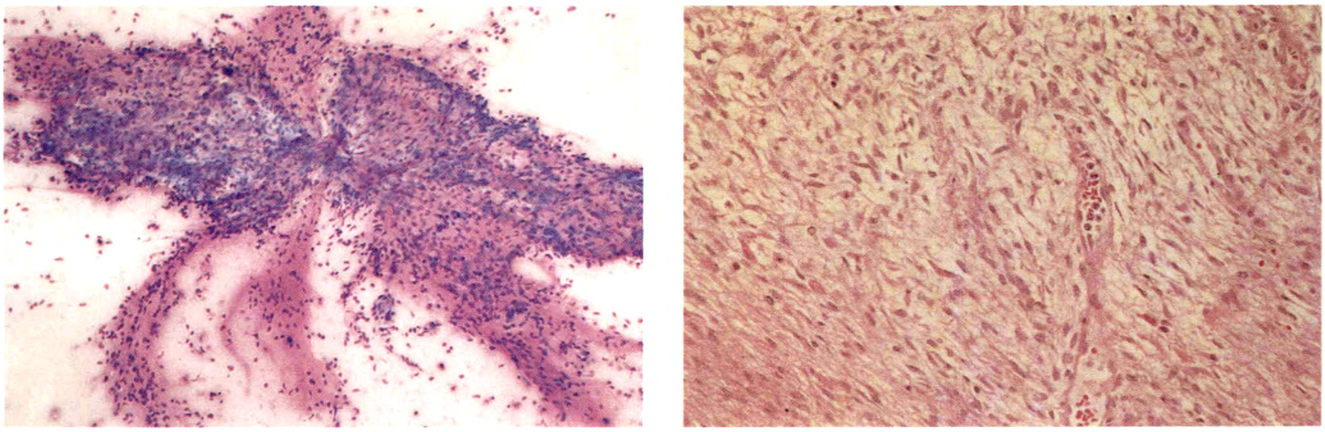

FIGURE 4. (A) A smear showing spindle-shape cells in a slightly mucoid background indicating a stromal pattern of WT. Diff-Quik stain 100x. (B) Histologic section for WT with a predominant stromal pattern. Hematoxylin and eosin stain 100x.

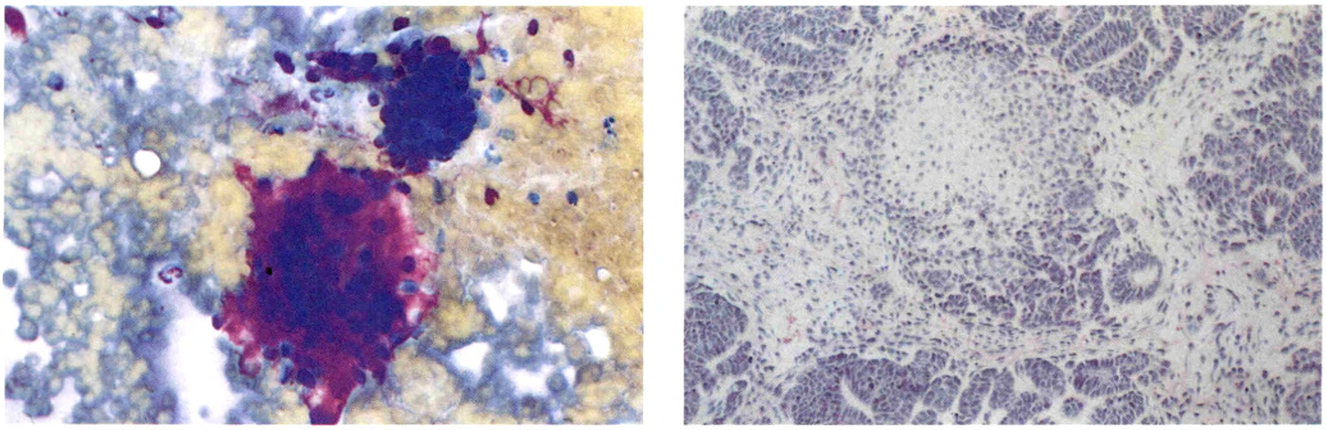

FIGURE 5. (A) Smear showing an area of cartilaginous differentiation within the stroma of WT. Diff-Quik stain 100x. (B) Histologic appearance of WT with cartilaginous differentiation. Hematoxylin and eosin stain 100x.

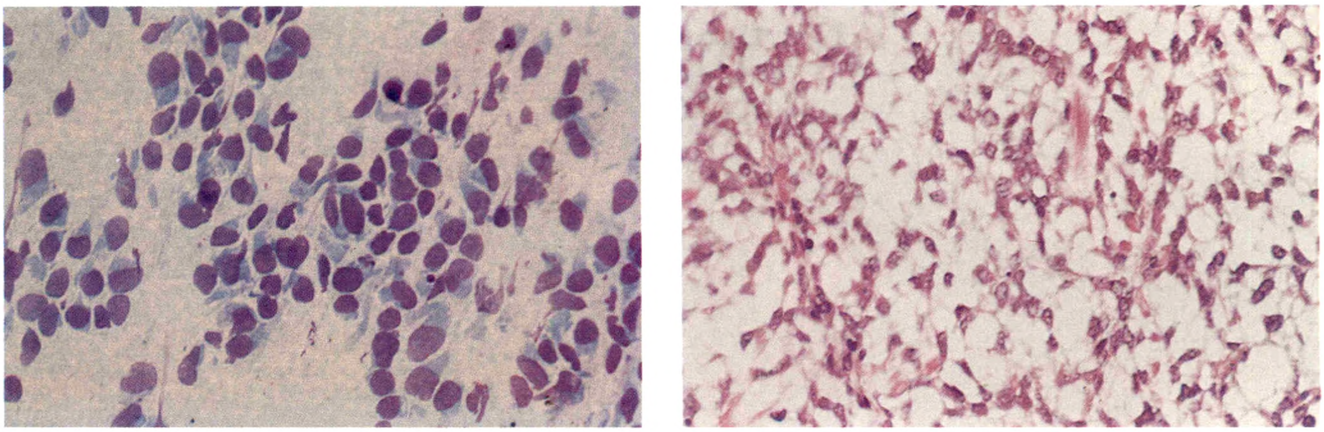

FIGURE 6. (A) Aspiration smear from a CSK featuring uniform cells that are loosely arranged in a slightly mucoid background. Diff-Quik stain 150x. (B) Histologic section showing clear cell pattern in CCSK. Hematoxylin and eosin stain 100x.

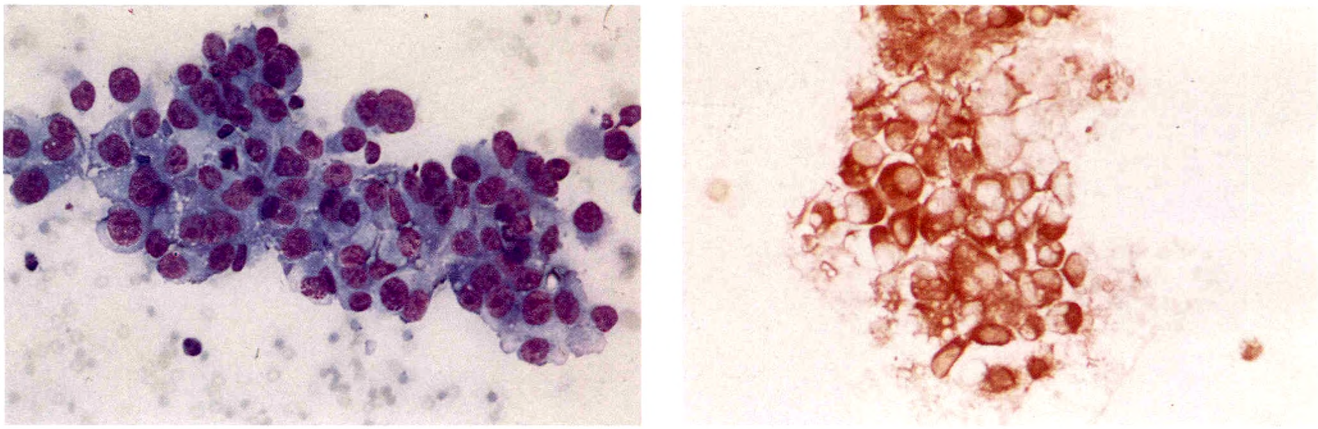

FIGURE 7. (A) A loosely arranged cluster of cells in aspiration smear from MRTK. The nuclei are round and large with well-developed nucleoli. Cytoplasm is moderate in amount and light blue. Diff-Quik stain 200x. (B) FNAB material from MRTK stained for vimentin. Immunoperoxidase staining 200x.

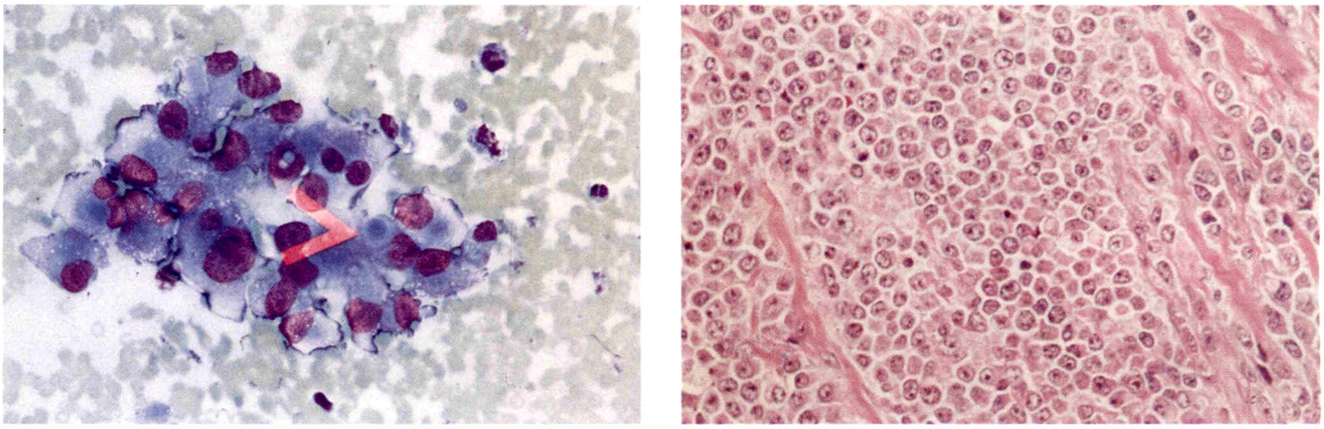

FIGURE 8. (A) Another cluster of cells from MRTK. Some of the cells show inclusion-like areas within the cytoplasm (arrow). Diff-Quik stain 200x. (B) Histologic section depicting a typical area within MRTK. Many of the tumor cells contain hyalinized inclusions within the cytoplasm. Hematoxylin and eosin stain 150x.

predominantly of round to polygonal tumor cells with large vesicular nuclei and prominent nucleoli. Mitosis may be frequent. The cytoplasm is moderate in amount and usually slightly eosinophilic. Within the cytoplasm of some of the tumor cells, variably sized hyalinized inclusions are present. These "rhabdoid cells" form the morphologic hallmark of MRTK (Figure 8B). Ultrastructurally, the inclusions in rhabdoid cells are composed of intermediate filaments. In the FNAB smears, the tumor cells are arranged in variably sized sheets and clusters of polygonal cells with large vesicular nuclei containing well-developed large nucleoli (Figures 7A).[11,12] In the Diff-Quik stained smears, the cytoplasmic inclusions are somewhat difficult to recognize but may be easily visualized in smears stained by hematoxylin and eosin stain or Papanicolaou stain (Figure 8A). These inclusions may also be recognized by staining the cells for vimentin (Figure 7B). Electron microscopy may also play a crucial role in recognition of these features including the filamentous cytoplasmic inclusions (Figure 9).

Congenital Mesoblastic Nephroma (CMN)

This tumor is typically seen during the first three months of life as a large unilateral renal mass.[1,24,25] Histologically, it is composed of interlacing bundles of uniform spindle-shape cells intermixed with renal parenchyma. The tumor cells have morphologic features ranging from fibroblasts to smooth muscle cells. Variable numbers of mitoses may also be present. In some cases, part or all of the tumor may contain poorly differentiated, highly cellular areas. These are usually designated as atypical CMN.[26,27] FNAB findings in CMN have been described in two case reports that revealed clustered and dyshesive spindle and tadpole shape cells with round to oval nuclei having small nucleoli. The cytoplasm of these cells was dense and homogeneously stained. The background was composed of mucoid fibrillar material.[28,29]

Cystic Nephroma (multilocular cyst)

This is an uncommon benign mass occurring in the kidney.[4] Histologically, it consists of cystic spaces separated by fibrous septa. The cysts are lined by cuboidal epithelium. Only one report of FNAB diagnosis of this lesion has been published.[30] The smear in this case revealed small sheets and clusters of small uniform epithelial cells with a slightly mucoid background.

Cystic Partially Differentiated Nephroma (CPDN)

This tumor has a gross appearance similar to that of cystic nephroma.[5] However, histologically there is a poorly differentiated cellular component within the fibrous septa separating the cystic spaces. These cellular elements are morphologically similar to WT. The prognosis of this tumor is excellent. FNAB findings in CPDN have not yet been reported.

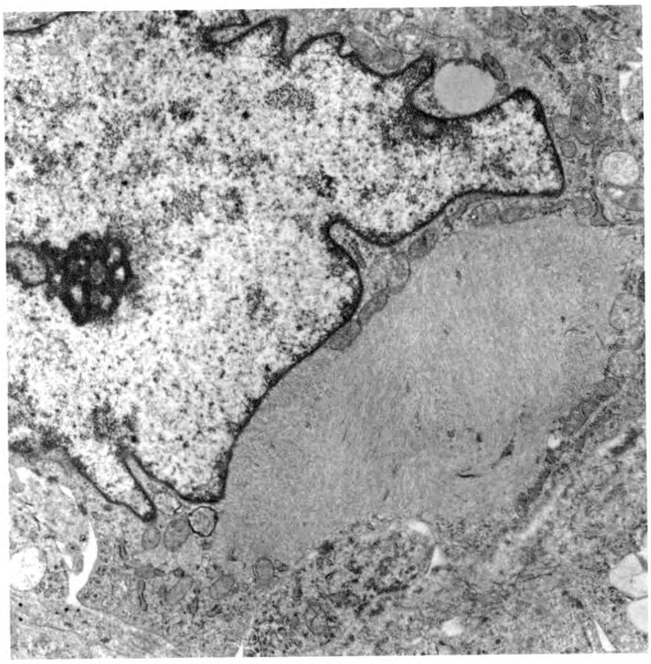

FIGURE 9. Electromyograph showing a rhabdoid cell containing a large aggregate of intermediate filaments. Uranyl acetate and lead citrate stain 5000x.

Renal Cell Carcinoma

Renal cell carcinomas are rarely encountered in children and young adults.[1,31,32] Renal carcinoma in children present at a later age than WT (mean age 9.8 versus 3.7 for WT). The histologic appearance of these tumors is identical to that seen in adults. However, occasionally neoplasms with morphology intermediate between renal carcinoma and Wilms' tumor may be encountered.[33] FNAB features of these tumors have not yet been described.

The diagnosis of most of the above-mentioned renal neoplasms may be possible on the basis of FNAB, provided clinical and radiologic findings are taken into full consideration. In some cases, especially where the tumor is poorly differentiated or clinical presentation is unusual, morphologic evaluation alone may not be sufficient for arriving at a precise diagnosis. In these cases, additional studies involving immunohistochemistry and electron microscopy may be used. Immunohistochemistry is especially helpful in the diagnosis of MRTK where a strong staining of the tumor cells for vimentin is noted. Furthermore, the cytoplasmic inclusion usually stains more intensely for vimentin than the surrounding cytoplasm. These inclusions may also be easily seen by electron microscopy as aggregates of intermediate filaments (Figure 9). In WT, electron microscopy may help establish the diagnosis by providing conclusive evidence of epithelial and tubular differentiation within the neoplasm. In a small number of cases, a definitive diagnosis of the renal mass may not be possible in spite of detailed immunohistochemical and electron-microscopic studies. In these cases, a tissue biopsy for histologic examination may be required.

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UNUSUAL COMPLICATION OF GASTROSTOMY

Ahmed H. Al-Salem, FRCSI, FICS

Tube gastrostomy is the preferred route for prolonged enteral feeding; however, it is associated with complications. This report describes an unusual complication of tube gastrostomy. Two of the most common complications of tube gastrostomy are intraperitoneal leak leading to peritonitis and distal migration of gastrostomy tubes to the pylorus, producing gastric outlet obstruction.[1,2] Unusual reported complications include perforation of the stomach,[1,3] esophagus,[1] duodenum,[4] intussusception,[5] and stomach prolapse at the gastrostomy tube site.[3,6] A case is presented of circumferential tear of the first part of the duodenum caused by gastrostomy tube and successfully managed by primary repair.

Case Report

A 57-day-old male, a product of a full term, normal, spontaneous vaginal delivery was diagnosed as a case of esophageal atresia immediately after birth. He was operated on at the age of two days and a gastrostomy was performed. Contrast studies via the gastrostomy catheter (Foley #10 French, Norta with balloon inflated to 4 cc) demonstrated esophageal atresia with a gap of about 3 1/2 vertebrae between the upper and lower pouches. He was treated conservatively with continuous upper pouch suctioning and feeding via gastrostomy. At the age of 26 days, he underwent primary end-to-end esophageal anastomosis. During surgery, he was found to have a blocked fistula from the lower pouch to the trachea, which was divided, and it was possible to perform end-to-end esophageal anastomosis under some tension. Postoperatively, he demonstrated a patent esophagus, but a severe non-dilatable stricture developed, subsequently leading to complete esophageal obstruction. At the age of 57 days, he was noticed to be unwell, tachypneic and febrile with mild epigastric distention. The gastrostomy feedings were discontinued. On the second day, the epigastric distention was still present and the gastrostomy catheter was not draining. His abdominal x-ray (Figure 1) revealed soft tissue density representing the dilated stomach displacing the bowel, and abdominal ultrasound revealed free fluid in the peritoneal cavity. The decision was made to perform a Gastrografin study via the gastrostomy, which showed a distally displaced catheter (Figure 2) into the duodenum and further contrast injection revealed a leak from the duodenum (Figure 3). The patient was operated on and was found to have a circumferential tear of the first part of the duodenum at the site of the balloon of the Foley catheter. This was repaired end-to-end in two layers. Postoperatively the patient did well and was restarted on gastrostomy feeding on the seventh postoperative day. He subsequently underwent resection of the esophageal stricture with end-to-end anastomosis and is doing well.

Discussion

Gastrostomy in infants and children is a common surgical procedure and a convenient and reliable route for feeding, especially in patients with esophageal atresia with a long gap while awaiting definitive surgery. Even though it is usually of a temporary nature and simple to construct, it is associated with a significant number of complications that lead to morbidity and in some, mortality.[1,2]

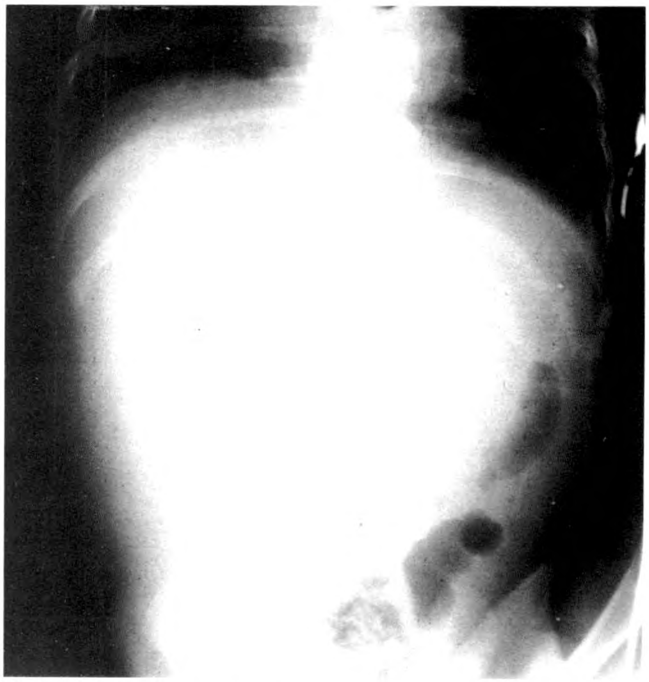

FIGURE 1. Plain x-ray of the abdomen demonstrated the dilated stomach and displacement of the bowel.

Address reprint requests and correspondence to Dr. Al-Salem: P.O. Box 6078, Dammam 31442, Saudi Arabia.

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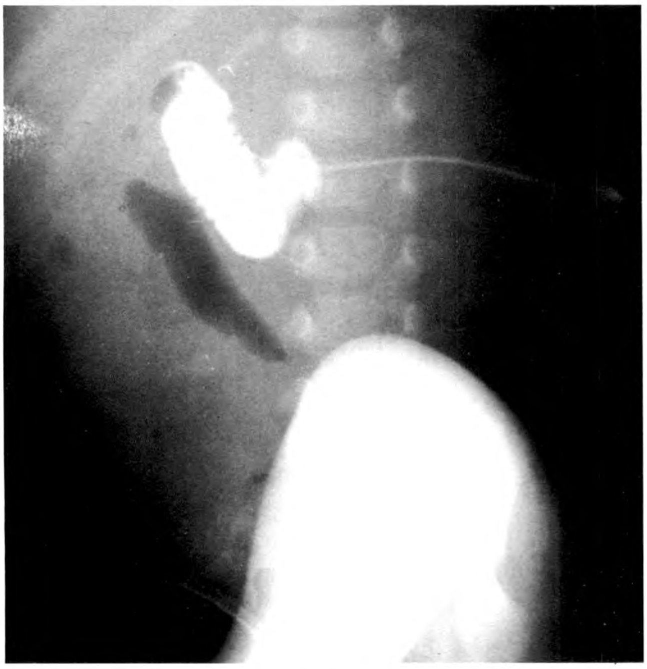

FIGURE 2. Gastrografin study via the gastrostomy demonstrating a distally placed Foley catheter into the duodenum.

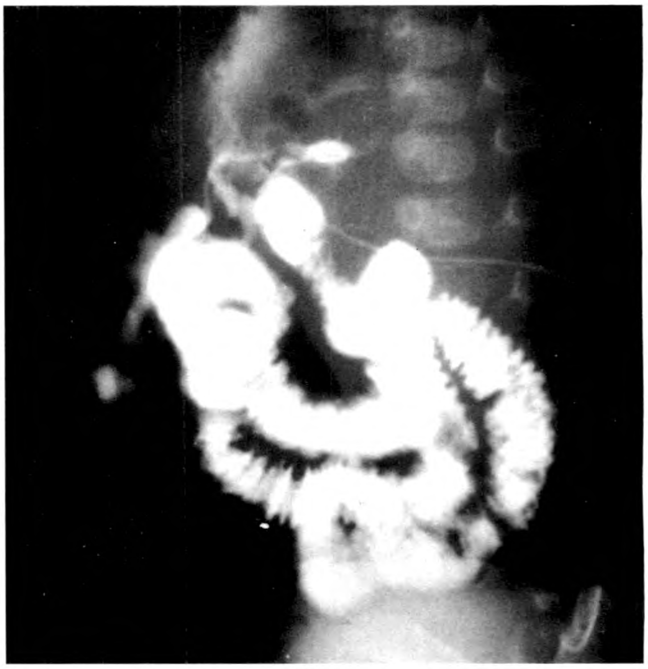

FIGURE 3. Gastrografin study via the gastrostomy demonstrating leakage from the duodenum.

One of the most common complications of tube gastrostomies is progression of the tube towards the pylorus and duodenum, producing gastric outlet obstruction. This is seen more commonly with Foley catheters and the presentation is that of repeated attacks of vomiting which are simple to treat by deflating and drawing the tube back into the stomach. Our patient had esophageal stricture and so it was not possible to detect this early, as there was no vomiting and the tip of the Foley catheter was already in the duodenum and was not draining. The only positive finding was the epigastric distention due to the dilated stomach. As a result of delay in recognition, I feel the balloon of the catheter exerted circumferential pressure necrosis to the first part of the duodenum, leading to complete disruption of the duodenum.

Simple duodenal perforation should be managed by primary closure, but larger defects should be repaired by a jejunal serosal patch or drainage by a Roux-en-Y jejunal loop because of the high incidence of anastomotic leakage and fistula formation after primary repair. Ballinger et al[4] described perforation of the lateral wall of the duodenum at the level of the ampulla of Vater in a case caused by gastrostomy tube that required jejunal overlay to close. In spite of the delay (as our patient came to operation over 24 hours following perforation), a primary anastomosis appeared possible and this was achieved as a two-layer closure.

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DUODENAL TUBERCULOSIS MIMICKING CARCINOMA, HEAD OF PANCREAS

Khaqan Jehangir Janjua, FRCS(Ed)

A 45-year-old Saudi male presented with a clinical picture of gastric outlet obstruction. Endoscopy showed pyloric stenosis with nonspecific inflammatory changes on biopsy. Ultrasound and computed tomography (CT) scan of the upper abdomen persistently demonstrated a mass in the head of the pancreas. Barium studies of the upper gastrointestinal tract showed markedly narrowed first part of the duodenum. On laparotomy, the pancreas was found to be normal, while a mass was present in the proximal part of the duodenum. Biopsy of the mass revealed a picture of duodenal tuberculosis. This case report points out the limitations of clinical evaluations and investigations in diagnosing duodenal tuberculosis and stresses the value of laparotomy and tissue diagnosis.

Case Report

A 45-year-old Saudi male was admitted to King Khalid University Hospital (KKUH) for dyspepsia, epigastric pain, anorexia, and weight loss of nine months' duration. He lost about 20 kg of weight within nine months. His complaints started with jaundice accompanied by dyspepsia and vomiting after meals. There was no change in bowel habits, but he gave a history of dark colored urine and clay colored stools. Jaundice resolved with outdoor treatments in different clinics and he was ultimately admitted to KKUH nine months after the appearance of jaundice.

While under investigation, he left the hospital against medical advice and was admitted to Riyadh Armed Forces Hospital (RAFH).

Nothing was found to be contributory from his history, family history or social history except that he was a smoker for 30 years of 20 cigarettes per day one year previously.

The physical examination revealed a cachectic male with a temperature of 37.5°C and a pulse of 80 beats per minute. Blood pressure was 120/80 mg/Hg. There was no icterus, lymphadenopathy or clubbing. Heart and lungs were normal. Abdominal examination revealed tenderness in the epigastrium but no mass or organomegaly was felt anywhere.

Investigations revealed a hemoglobin of 13.2 g/dl and a total leukocyte count of 5.8×10^9/L (polymorphs). Erythrocyte sedimentation rate (ESR) was 12 mm during the first hour. The Mantoux test was strongly positive (20 mm x 30 mm) using 1 x 10,000 tuberculin units. Liver function tests showed proteins 83 g/L, albumin 40 gm/L, AG ratio 0.9, total bilirubin 15 µmol/L, alkaline phosphatase 147 u/L, AST 48 u/L (11-55). Chest x-ray was normal. Ultrasound of the abdomen was inconclusive. The pancreas was not visualized.

CT scan of the abdomen showed intrahepatic bile duct dilatation and a mass in the head of the pancreas, measuring 5.2 cm x 3.3 cm in size (Figure 1). There were enlarged para-aortic lymph nodes. Upper gastrointestinal tract (GIT) endoscopy showed redness of antral mucosa and deformed rigid pylorus. There was a gross deformity of the bulbar mucosa with edema, ulceration, and contact bleeding. It was difficult to advance the endoscope beyond the proximal part of the bulb. Repeat endoscopy a month later revealed prepyloric erosions and stenosis of the pylorus, because the endoscope was unable to pass beyond the antrum.

An upper gastrointestinal barium study revealed marked distention of the stomach with food residue and prolonged delay of gastric emptying. The duodenum was markedly narrowed, especially the first part (Figure 2). There was not enough contrast in the small bowel. CT-guided fine needle aspiration (FNA) of the mass in the head of the pancreas was not conclusive. Endoscopic biopsy of

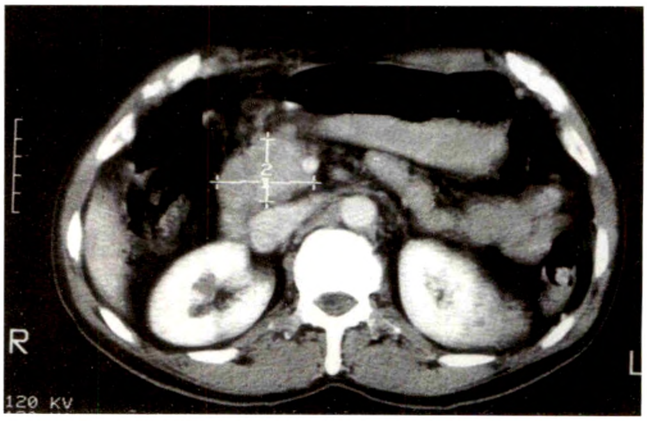

FIGURE 1. Computed tomographic scan of mass in the head of the pancreas.

Address reprint requests and correspondence to Dr. Janjua: 136 Esme Road, Spark Hill, Birmingham B11 4NN, U.K.

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gastric erosions showed chronic nonspecific gastritis. Gastric washings for acid-fast bacilli (AFB) were negative. A provisional diagnosis of gastric outlet obstruction because of extrinsic compression, most probably due to carcinoma of the head of the pancreas, was made. At laparotomy, a mass was felt in the pylorus and first part of the duodenum. Adhesions around the mass were released and a wedge biopsy was taken from the mass. The pancreas showed no mass or any other gross abnormality. The liver was normal in appearance and feel. The mass was bypassed by anterior gastrojejunostomy.

Histopathology of the tissue revealed the duodenum involved in granulomatous inflammation. The Langhan's giant cells were present, but no bacilli were identified under microscopy.

On the basis of the prevalence of tuberculosis in this part of the world, histology findings and strongly positive Mantoux test, a final diagnosis of tuberculosis of the duodenum was established and the patient was placed on antitubercular drugs. He made a good recovery and was discharged after 10 days.

He was readmitted 45 days later with a clinical picture of intestinal obstruction. Provisionally, adhesions around the gastrojejunostomy were suspected, but on Gastrografin studies, the gastrojejunostomy was patent. The duodenal stricture had responded well to antitubercular treatment, as the duodenum was patent and contrast was seen to pass through the pylorus into the duodenal loop (Figure 3). An erect film suggested distal bowel obstruction. At laparotomy, a band of fibrous tissue was found obstructing the small bowel at approximately 10 cm from the ileocecal valve. The band was divided and the bowel freed.

The patient recovered smoothly over nine months of antitubercular therapy and follow-up. His health continuously improved with a weight gain of 8 kg.

Discussion

Gastrointestinal tuberculosis is still a common disease in Saudi Arabia, despite development of the health care system. The duodenum remains the rare site of gastrointestinal tuberculosis; its involvement accounts for only 2.5% of tuberculous enteritis.[2] In a study at Riyadh Armed Forces Hospital, the incidence of tuberculosis of the ileocecal region was 56.6%, colon 18%, stomach 5.4%, and esophagus 1.8%.[1] In the duodenum, the most common portion to be involved is the third part. Involvement of the first part is often contagious with similar lesions involving the stomach.[6] With our patient, the first part of the duodenum was involved without affecting the stomach. Isolated tuberculosis of the duodenum is rare, probably because of the rapid transit time taken by gastric contents to travel through the duodenum.[3,5] Tuberculous duodenal obstruction is usually secondary to lymph node involvement causing extrinsic compression.[4] In the present case, duodenal obstruction was due to hyperplastic tuberculous lesions of the duodenum instead of lymph node involvement.

There is no typical presentation of duodenal tuberculosis. Patients often complain of epigastric pain, nausea, vomiting, and weight loss. Usually it mimics peptic ulcer disease and presents with gastric outlet

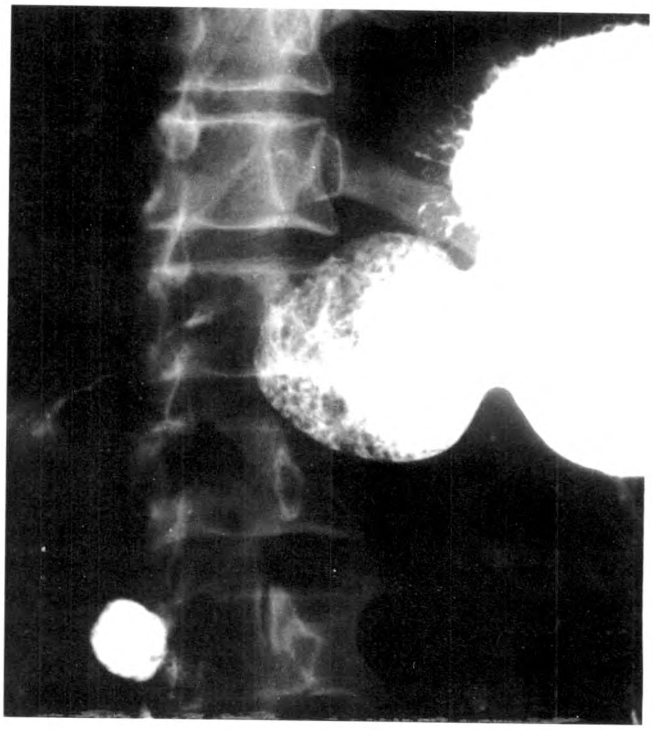

FIGURE 2. Barium meal examination showing stricture of duodenum.

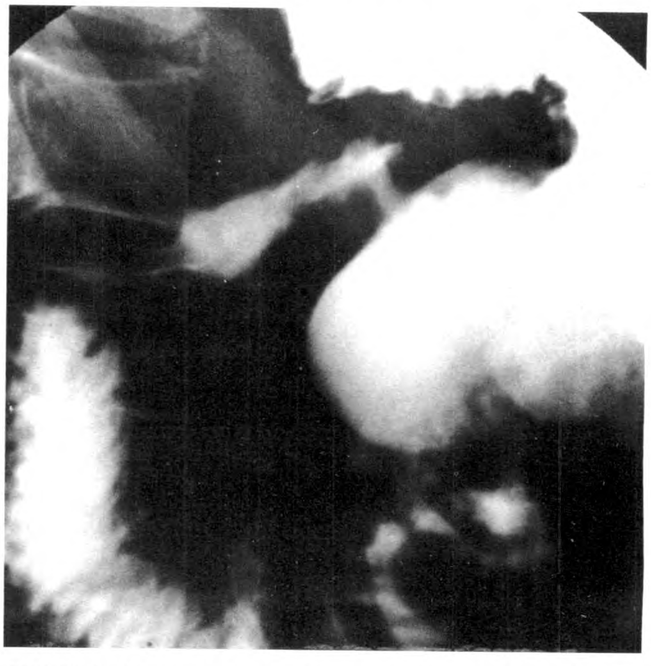

FIGURE 3. Gastrografin study of upper gastrointestinal tract showing patent duodenal loop.

obstruction, but other unusual presentations are: upper GI bleeding,[7] obstructive jaundice,[8] and enterorenal fistula.[9] Our case presented with vague upper gastrointestinal symptomatology and delayed gastric emptying, while during investigations, a mass in the head of the pancreas was found, causing extrinsic compression of the duodenum. As endoscopic and CT-guided biopsies were not conclusive and carcinoma of the head of the pancreas could not be ruled out, laparotomy was performed to obtain the diagnosis and bypass the obstruction. Intraoperative frozen sections were not sent, but may be of help to avoid extensive resections.[10]

In conclusion, it can be emphasized that in endemic areas, duodenal tuberculosis should be considered as one of the causes of gastric outlet obstruction, even in the absence of pulmonary tuberculosis. In patients in whom the clinical and macroscopic picture suggests malignancy, it is important to have intraoperative diagnosis by frozen section to avoid unnecessary radical surgery with its associated morbidity and mortality.

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CONGENITAL RECTAL STENOSIS: A SIMPLE APPROACH TO MANAGEMENT

Ahmed H. Al-Salem, FRCSI, FICS; Ahmed Al-Faraj, MBBS; Vasant Talwalker, FRCS

Rectal atresia is a rare type of high anorectal malformation and of the variants of rectal atresia, congenital rectal stenosis is the least common type.[1] Various surgical procedures[2-5] have been described for the management of rectal atresia, but due to its rarity, there is no standard tested approach for its management. We present a case of congenital rectal stenosis in a 3-1/2-year-old female and describe a simple technique for its management.

Case Report

A 3-1/2-year-old female was referred to Qatif Central Hospital because of soiling her pants with liquid stools since birth, and just prior to her presentation, she started to complain of abdominal pain and distention. On examination, she was found to have mild abdominal distention with palpable fecal masses in the abdomen. A hard fecaloma was palpated in the pelvis on rectal examination, while the rectum was empty. After repeated rectal washouts, it was noted that the fecaloma was in the proximal part of the rectum immediately above a diaphragm with a central hole about 3 cm from the dentate line. This was confirmed by a barium enema (Figures 1 and 2).

Surgical Technique

The patient underwent a laparotomy through a transverse suprapubic incision. The upper third of the rectum and sigmoid colon were dilated and hypertrophied, while the lower part of the rectum was normal in caliber and the junction between the two was clearly seen. There was no other pathology. The sigmoid colon was opened longitudinally to visualize the septum, which had a central hole. The #28 EEA gun (without anvil) was introduced transanally. The shaft was guided into the opening by a finger into the proximal rectum, through the opening in the sigmoid colon. The anvil was screwed on the shaft through the colotomy opening until it was flush at the site of the central hole. The gun was then fired. The head was released and the entire instrument was recovered from the

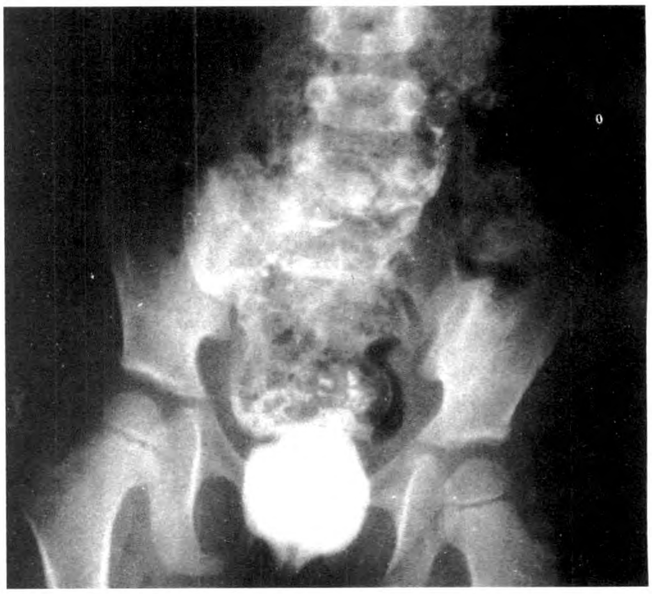

FIGURE 1. Barium enema, posteroanterior view of the abdomen showing the site of rectal stenosis with proximal colonic dilatation.

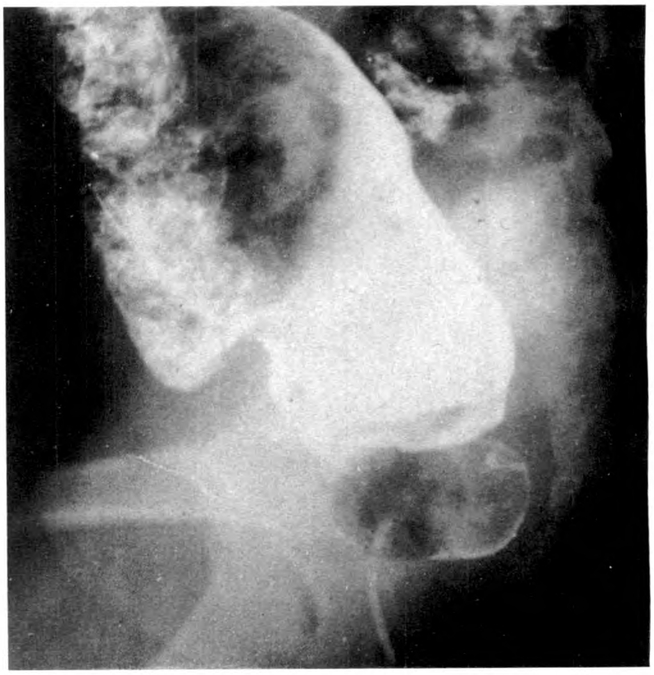

FIGURE 2. Barium enema, lateral view demonstrating the site of rectal stenosis with primal colonic dilatation.

From the Division of Pediatric Surgery, Department of Surgery, Qatif Central Hospital, Qatif.

Address reprint requests and correspondence to Dr. Al-Salem: P.O. Box 6078, Dammam 31442, Saudi Arabia.

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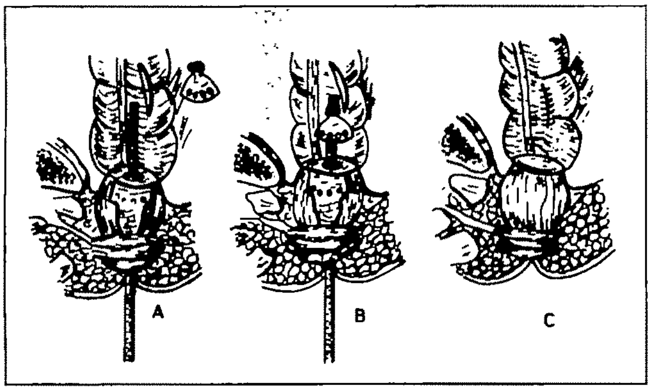

FIGURE 3. Operative resection of the rectal diaphragm using the EEA autosuture: a) the EEA gun without anvil is introduced transanally and the shaft guided into the opening in the diaphragm, guided by a finger into the proximal rectum and sigmoid colon. b) the anvil was screwed on the shaft through the colotomy opening until it was flush at the site of the central hole. c) the gun was fired, released and then recovered from the anus. The opening in the sigmoid colon closed.

anus (Figures 3a, b, and c). The gun contained a complete disc of tissue with a central opening. The integrity of the anastomosis was confirmed and the opening in the sigmoid colon was closed longitudinally in two layers.

The septum histologically was lined by stratified squamous non-keratinizing epithelium on the anal aspect and by rectal mucosa on the rectal side with an abrupt junction between the two. Beneath the epithelium there were striated muscle bundles arranged in a haphazard way without any clearly defined muscularis mucosa.

Postoperatively, the patient was passing stools easily without soiling but from time to time she required glycerin suppositories because of constipation. Rectal examination five months postoperatively revealed an adequate opening at the anastomosis site.

Discussion

Rectal atresia is a rare type of high anorectal malformation and its incidence worldwide is low.[1] Of the variants of rectal atresia, congenital rectal stenosis is the least common type. Dorairajan, in a series of 147 cases of rectal atresia, found only three cases of rectal stenosis.[1]

Congenital rectal stenosis has been classified either as a separate entity in the rare variants of high anorectal malformations[6] or, more accurately, as Type IV in the classification of rectal atresia proposed by Dorairajan.[1] Even though it has been classified as a variant of high anorectal anomalies, unlike them, the anal canal as well as the pelvic floor and surrounding sphincters is normally formed. Pathologically, congenital rectal stenosis actually resembles a duodenal diaphragm with a central hole, which is equivalent to Type I of colonic atresia according to the classification described by Sutton.[7] Congenital rectal stenosis due to extrinsic causes, e.g., presacral teratoma and anterior sacral meningocele, has been reported previously.[8]

The optimal goal in the management of cases of high anorectal agenesis is acquisition of continence. Various surgical techniques, some of which are major, have been described for the management of rectal atresia,[2-5] but because of its rarity, there is not a well proven and tested approach for its management. Congenital rectal stenosis, although a variant of rectal atresia, can be approached differently in its management. Cole[9] reported a 10-year-old male with rectal stenosis due to a congenital diaphragm placed 8 cm from the anal margin. This patient was treated initially by a loop colostomy and ultimately required resection and end-to-end anastomosis. The EEA staplers have been used extensively in gastrointestinal surgery including stricture resection,[10,11] but their use in the pediatric age group is limited. Our patient was operated upon successfully using a simple technique without interfering with the anatomy and function of the sphincters and obviating a long-term colostomy.

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THYROID ABSCESS CAUSED BY INTERNAL FISTULA

Ahmed H. Al-Salem, FRCSI, FICS; Hussain A. Abu-Srair, FRCP(C), FAAP;
Ali M. El-Bashier, FRCPath

Acute suppurative thyroiditis is an uncommon condition, particularly in the pediatric age group.[1,2] The routes through which bacteria reach the thyroid may be the blood stream, the lymphatics, a persistent thyroglossal duct, direct trauma to the thyroid gland, and direct invasion from neighboring structures.[3] However, in most cases the route of infection is not obvious. In this respect, we describe a rare case of congenital fistula originating at the pyriform sinus as a route of infection in acute suppurative thyroiditis.

Case Report

An eight-year-old-Saudi female was admitted to Qatif Central Hospital with a seven day history of painful swelling of the left side of the neck associated with fever and difficulty swallowing. She gave a history of an upper respiratory tract infection a few days prior to the appearance of the swelling.

On examination, she was febrile and looked ill (T 38.5°C). Examination of the neck revealed a red, warm and tender swelling mainly on the left side (Figure 1). This swelling measured 4x3 cm and moved with swallowing. Her complete blood count (CBC) showed a hemoglobin of 11.8 g/dl, white cell count of 9.4×10^9/L with 69% polymorphs. The erythrocyte sedimentation rate (ESR) was 104 mm/hr and blood cultures were negative. Her T3 was 1.77 mg/dl (n=15.5) and T4 was 1.18 mg/dl (n=0.8-1.8). Thyroid antibodies were negative. Neck ultrasound showed a fairly large hypoechoic area with a central area of increased echoes involving the left lobe of the thyroid, representing the abscess cavity and measuring 3.8x2.5 cm. The diagnosis of acute suppurative thyroiditis was established and the patient was initially treated with intravenous crystalline penicillin 100,000 units/kg/24h given every four hours and intravenous cloxacillin 100 mg/kg/24h in four divided doses for four days, but there was no improvement. A needle aspiration was performed. This revealed pus and about 15 cc were aspirated. The antibiotics were changed to intravenous cefuroxime (Zinacef) 100 mg/kg/24h in four divided doses and Flagyl 250 mg every eight hours for another five days, but the patient was still febrile and the swelling was becoming larger. A computed tomography (CT) scan of the neck (Figure 2) showed a fairly large soft tissue density involving the left lobe of the thyroid gland with multiple

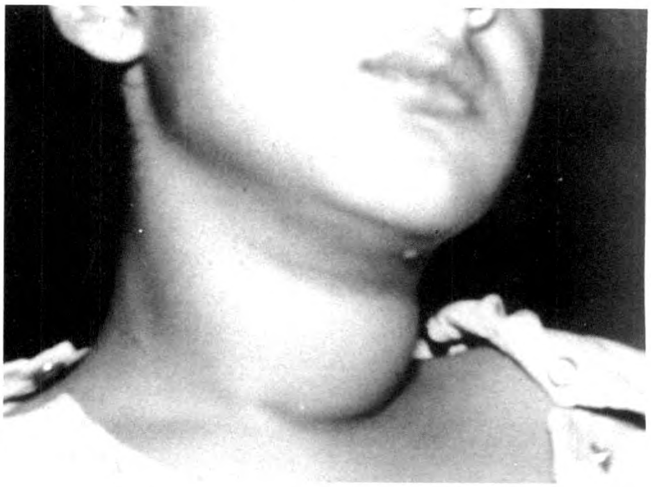

FIGURE 1. Eight-year-old female with a left-sided thyroid abscess.

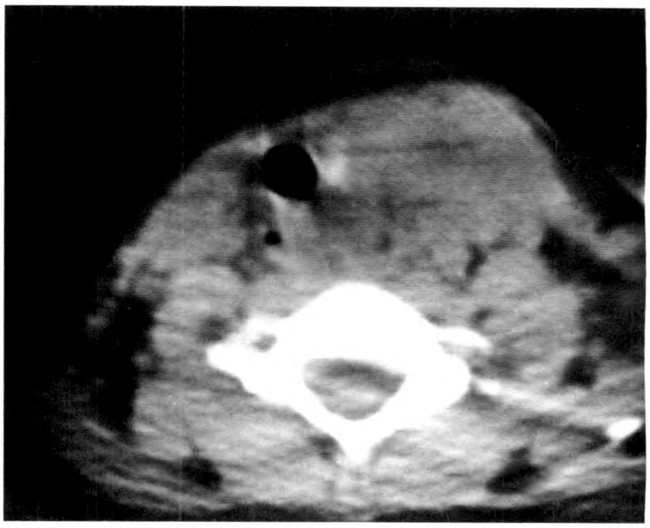

FIGURE 2. CT scan of the neck showing a large soft tissue density mass involving the left lobe of the thyroid gland with multiple pockets of air trapped within the soft tissues.

From the Division of Pediatric Surgery, Department of Surgery (Dr. Al-Salem); Department of Pediatrics (Dr. Abu-Srair); Department of Microbiology (Dr. El-Bashier), Qatif Central Hospital, Qatif.

Address reprint requests and correspondence to Dr. Al-Salem: P.O. Box 6078, Dammam 31442, Saudi Arabia.

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pockets of air trapped within the soft tissues and extending from the parapharyngeal region of the retropharyngeal area. The patient underwent incision and drainage and about 50 ml of pus were drained. Microscopic examination of the pus revealed white blood corpuscles with minute gram positive cocci. Pus was cultured on blood agar, chocolate agar aerobically and blood agar anaerobically. After 24 hours' incubation, *Streptococcus milleri* was identified by the characteristic sweetish caramel smell, colony morphology, and catalase test; identification was confirmed by A.P. 1.20 Strep. (API system SA, La Balme-Les-Grottes, France) and by streptex grouping (Wellcome Research Laboratories, England). The patient was restarted on intravenous crystalline penicillin and she did well and was discharged home in good condition.

On follow-up four weeks following her discharge from the hospital, a barium swallow was done (Figure 3). This revealed a well-defined fistula tract extending from the apex of the left pyriform sinus for 3.5 cm and ending blindly in a small pouch.

The patient is six months postoperative and doing well. She is being followed up in the outpatient department and is to be admitted for excision of the fistula.

Discussion

Acute suppurative thyroiditis is much less common than other types of thyroiditis. In 1973, Kirkland et al[4] reviewed 36 cases of thyroid abscess in children, only five of which have been documented in the English literature since 1950. The rarity of acute suppurative thyroiditis may be due to the remarkable degree of local resistance of the thyroid gland to bacterial infection. This has been demonstrated by Womach and Cole,[5] who injected cultures of streptococcus directly into the superior thyroid arteries of dogs but produced fewer infections. The gland's capsule probably prevents local infection in the neck from extending into it. Also the relatively high concentration of iodine within the thyroid gland may provide an unfavorable environment for bacterial growth.

Although several routes through which bacteria reach the thyroid gland have been described,[3] the route is unknown in most cases. Pyriform sinus fistula as a route of infection in acute suppurative thyroiditis has been increasingly reported.[6-9] The fistula extends from the apex of the pyriform fossa anteroinferiorly into the semi-closed space surrounding the thyroid gland, and so infection through the fistula results in a perithyroid infection that spreads to involve the thyroid gland, leading to acute suppurative thyroiditis that can progress to abscess formation. This pyriform sinus fistula has been described as a remnant of the fourth pharyngeal pouch by several authors,[7,8] but recently it has been considered to be of third branchial or pharyngeal pouch origin. Embryologically both the third and fourth pharyngeal pouches may pursue a similar route into the pyriform fossa.[10] Interestingly, the occurrence of this fistula has been reported almost exclusively in Japanese.[1,7-9] This is the first documented report of its occurrence in a Saudi child. The exclusively left-sided occurrence of the fistula is not completely understood.

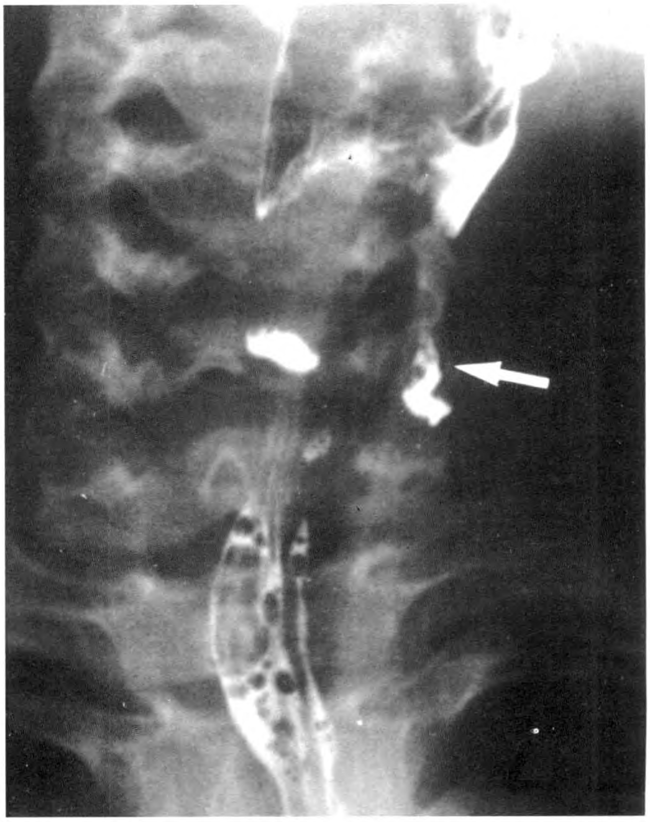

FIGURE 3. Barium swallow demonstrating an internal fistula (arrows) originating from the left pyriform sinus. Note also the presence of multiple small diverticular lesions in the upper esophagus.

Another interesting aspect of this case is the infecting organism. Several organisms may cause acute suppurative thyroiditis. The most common bacteria involved are *Hemolytic streptococcus*, *Staphylococcus aureus*, and Pneumococcus.[3] Anaerobic bacteria such as Bacteroides, Peptostreptococcus and Peptococcus were also identified as causative organisms of acute suppurative thyroiditis.[1,4] Tuberculosis may also be involved in thyroid abscess formation.[11] The causative organism in our patient was *Streptococcus milleri*. This includes members of Lancefield's Group F, certain minute colony-forming members of Group A, C, G and non-groupable beta-hemolytic streptococci, together with organisms described as "*S. intermedius*".[12] The natural habitat of *S. milleri* is the respiratory and gastrointestinal tracts and vagina.[13,14] It has been reported to cause meningitis, liver abscess, central nervous system infections, peritonitis, arthritis, maxillary sinusitis, and intra-abdominal sepsis.[15,16] This is the first report of *S. milleri* as the causative organism of acute suppurative thyroiditis.

The possibility of this fistula must be considered in a child who presents with acute suppurative thyroiditis, particularly in patients experiencing recurrent episodes or in those with organisms that are part of the oropharyngeal flora. A careful examination of the hypopharynx including barium swallow is necessary to identify the pyriform fossa fistula. Makino et al[17] were able to demonstrate this fistula by endoscopic insertion of a Fogarty catheter through the pyriform fossa. Complete extirpation of the fistula results in a permanent cure and prevents the recurrence of this disease.

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ODONTOID HYPOPLASIA, ATLANTO-AXIAL INSTABILITY AND CERVICAL MYELOPATHY IN PSEUDOACHONDROPLASIA

Neville A. Russell, MD, FRCS(C); CR Hamdy, MD, ChB;
Brien G. Benoit, MD, FRCS(C); Garry J. Belanger, MD, FRCP(C)

Pseudoachondroplastic dwarfism (PAD) is second only to achondroplasia as a cause of short limb dwarfism. It is a spondylo-meta-epiphyseal dysplasia, characterized by normal intelligence and craniofacial appearance, late diagnosis of dwarfism, marked ligamentous laxity and joint instability, lower limb abnormalities and a variable degree of vertebral column involvement.[1] Congenital hypoplasia of the odontoid has been well documented in PAD.[2] This anomaly, in combination with the inherent ligamentous laxity, may lead to atlanto-axial instability. We report the case of an adult with PAD and odontoid hypoplasia who developed C1-C2 subluxation and severe quadriparesis. Improvement occurred after posterior C1-C2 fusion. Although odontoid hypoplasia and atlanto-axial instability are relatively common in PAD, cervical myelopathy is rare.

Case Report

Two years prior to hospital admission, a 27-year-old female with PAD experienced the spontaneous onset of gradually progressive generalized weakness and easy fatigability. This progressed over several months until she could no longer walk. Her upper limbs were less affected and she was able to manage the ordinary activities of daily living. Three months prior to admission, the upper limb weakness worsened and rapidly progressed. The weakness was so severe that she became totally dependent, not even being able to manipulate the controls of her electric wheelchair. She had occasional urinary hesitancy and constipation, but no other symptoms to suggest sphincter dysfunction. Examination revealed obvious dwarfism and severe spastic quadriparesis. The power in all muscle groups was 2 to 3/5. Plantar responses were extensor and there was bilateral knee and ankle clonus. No sensory abnormality was detected. Anal tone was slightly reduced.

Basic hematological and biochemical investigations were normal. Cervical spine radiographs showed marked hypoplasia of the odontoid and this was confirmed by lateral tomography (Figure 1A). The distance between the posterior aspect of the anterior arch of C1 and the odontoid measured 9 mm. Correspondingly, the distance between the anterior aspect of the posterior arch of C1 and the odontoid measured 11 mm. Flexion extension views were not obtained because of the patient's inability to cooperate. Computerized tomography (CT) following metrizamide myelography demonstrated compression anterior to the spinal cord at the C1-C2 level in relationship to the posterior displacement of C1. Also, a hyperdense soft tissue mass was noted, situated anteriorly, at the level of the tip of the hypoplastic odontoid (Figure 2). Management was complicated by the fact that the patient was extremely immature and her family very uncooperative. They refused to consider any attempt at reduction by skeletal traction. Discussion of occipitocervical fusion with postoperative stabilization in a halo apparatus or Minerva cast was met with similar refusal, on the grounds that she would not be able to cope.

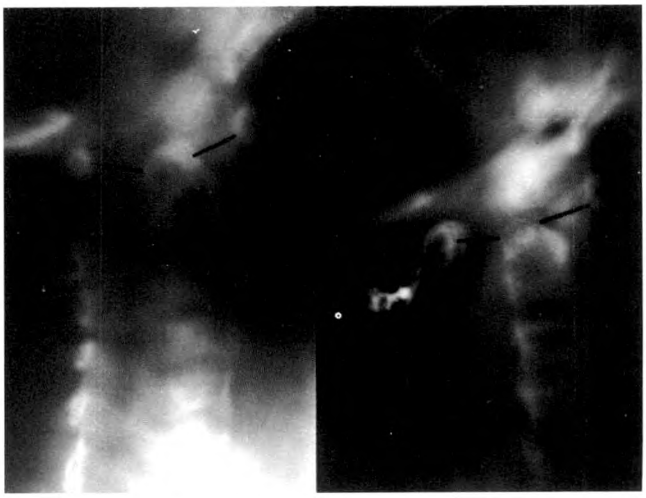

FIGURE 1. (A) Tomograms of the upper cervical spine showing odontoid hypoplasia. The AP diameter of the spinal canal at the level of the odontoid is markedly reduced (anterior black line). The distance between the odontoid and the anterior arch of the atlas is correspondingly increased (posterior black line). (B) Postoperative tomogram showing no change in these relationships (black lines).

From the Division of Neurosurgery, (Dr. Russell) King Fahad National Guard Hospital, Riyadh and the Division of Neurosurgery (Drs. Hamdy, Benoit) and the Department of Diagnostic Radiology (Dr. Belanger), Ottawa Civic Hospital and the University of Ottawa.

Address reprint requests and correspondence to Dr. Russell: Department of Surgery, King Fahad National Guard Hospital, P.O. Box 22490, Riyadh 11426, Saudi Arabia.

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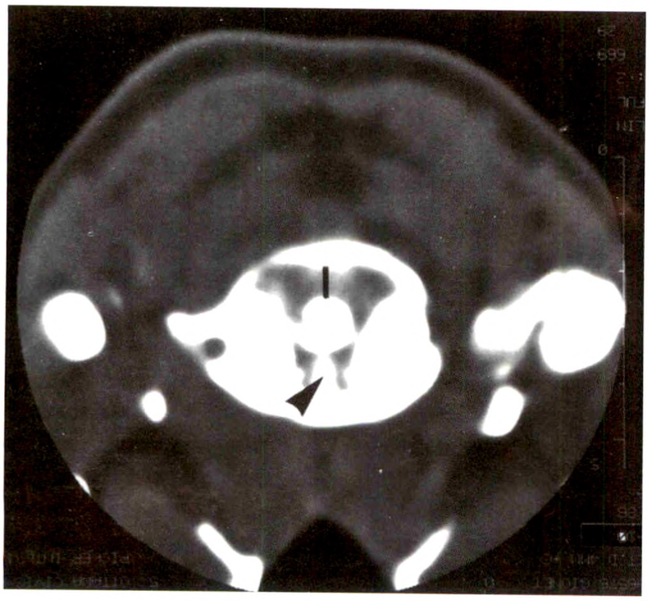

FIGURE 2. CT at the level of the tip of the hypoplastic odontoid showing marked reduction in the AP diameter of the spinal canal (black line) and an anteriorly placed hyperdense soft tissue mass (arrow).

They finally agreed to accept a posterior surgical fusion. We decided to proceed with this in an attempt to control the rapidly worsening neurologic deficit.

The operation was carried out under general endotracheal anesthesia. Intubation was first performed with the patient awake and care taken to maintain spinal alignment. Gardner-Wells skull tongs were inserted and skeletal traction applied using a three pound weight. Under portable x-ray control, the weight was increased by increments to nine pounds. At nine pounds, it appeared that reduction of the C1-C2 subluxation had been achieved, although the portable radiographs were of poor quality. A C1-C3 fusion was performed using a corticocancellous bone graft (iliac crest) and wire and the neck immobilized in a firm cervical collar. In the immediate postoperative period there was no change in her lower limbs, but there was dramatic improvement in her upper limb strength. However, repeat lateral tomography of the cervical spine showed no change in the C1-C2 subluxation (Figure 1B), indicating the reduction had not occurred prior to the fusion. At follow-up examination eight months later, her functional status had returned to the level that had existed prior to the onset of arm weakness She could manage the ordinary activities of daily living, turn in bed, transfer from bed to wheelchair with assistance, and manage the controls of her wheelchair without difficulty. There had been no improvement in her leg weakness.

She remained improved for approximately two years after the operation, when her condition began to deteriorate. Over one year, there was gradually worsening arm weakness, accompanied by severe burning paresthesias in all four limbs. Examination revealed severe spastic quadriparesis, i.e., virtually identical to that which was noted when she first presented. Plain radiographs of her cervical spine revealed no new abnormality. The wires that had been placed between C1 and C2 were intact. However, the expected bony fusion mass was not seen. She refused any further investigation or treatment.

Discussion

We found only three previous reports of cervical myelopathy occurring in association with PAD.[3-5] Ford et al[3] described the case of a 12-year-old female who became gradually quadriplegic after mild trauma. After two cervical laminectomies . . . "the patient stabilized with paraplegia". Kopits et al[4] reported a 10-year-old male who developed a cervical myelopathy that progressed over several years. Various lower limb deformities were surgically corrected but improvement in the quadriparesis did not occur until a C1-C2 fusion was performed. Another case, reported by Kuzume et al,[5] was that of a 14-year-old male with "chronic cervical cord myelopathy", paralysis and respiratory failure. No improvement followed "surgical treatment of atlanto-axial dislocation".

It may be difficult to predict which patients with atlanto-axial instability will develop cervical myelopathy. Hensinger, in a study of adult patients, suggested surgical stabilization for instability with more than 5 mm of anterior or posterior slippage.[6] However, Kopits, in a series of 231 dwarfs, including 31 with PAD, could show no correlation between the x-ray appearance of the upper cervical spine and the clinical findings.[2] There is general agreement that surgery is indicated for those patients who have recurrent or progressive neurological deficits, but the symptoms may develop insidiously, beginning with generalized weakness and easy fatigability. This may be present for a considerable period before pyramidal tract signs appear.[2,4] Usually the surgery consists of occipito-cervical or C1-C2 fusion using wire and bone graft, after first reducing the displacement by skeletal traction.[7,8] There are also advocates of transoral decompression of the odontoid and its ligaments combined with posterior stabilization.[9]

Our patient's spinal cord function improved after simple posterior fusion of C1-C3 without decompression. The early improvement may be attributed to the immediate stabilization effect of the wiring. An explanation for the continued improvement may be found in the work of Perovic et al[10] and Larsen et al.[11] The former,[10] in a radiological study of patients with congenital atlanto-axial dislocations, showed that narrowing of the spinal canal occurred mainly from the ventral aspect. They believed this to be due to thickening of the soft tissue posterior to the dysplastic odontoid and the body of the axis, i.e., where the posterior longitudinal ligament blends with the transverse atlantal ligament at the C1-C2 level. Abnormal motion at this level causes this normal structure to become hypertrophic. When the motion is suppressed by fusion, this soft tissue mass atrophies, thus increasing the spinal canal space. The latter[11] effectively tested this hypothesis when they treated a 56-year-old male with high spinal cord compression due to an undiagnosed odontoid fracture. Posterior fusion alone resulted in improvement of the neurologic deficit. Magnetic resonance imaging (MRI) studies demonstrated marked reduction in the size of an anterior mass caused by periodontoidal cicatrix. The CT metrizamide study in our patient demonstrated an anteriorly placed soft tissue mass that likely represented this cicatrix (Figure 2). Unfortunately, the patient would not permit subsequent studies so we were unable to confirm any change in its size.

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BROMOCRIPTINE-INDUCED CEREBROSPINAL FLUID RHINORRHEA IN INVASIVE PROLACTINOMA: CASE REPORT AND REVIEW OF THE LITERATURE

Neville A. Russell, MD, FRCSC; Saad Al-Rajeh, MD; Naif Al-Fayez, Facharzt;
Andrew J. Joaquin, MD, FRCSC; Asiru Abu Bakhr, MD, FRCPC

The occurrence of cerebrospinal fluid (CSF) rhinorrhea in association with pituitary gland tumors is an uncommon but well-recognized phenomenon. Although reported in untreated cases,[1] it is more likely to occur as a complication of surgery[2] or radiotherapy.[3] During recent years, evidence has accumulated to suggest that it may also develop during bromocriptine treatment of pituitary tumors, especially when this drug is used as an adjunct to surgery and/or radiotherapy.[4-7] However, it has also occurred when bromocriptine has been the only treatment.[8-12] In this report, we describe a patient who developed CSF rhinorrhea while receiving bromocriptine treatment for a prolactin-secreting pituitary tumor in the absence of prior surgery or radiotherapy. We also reviewed 15 similar cases obtained from the literature.

Case Report

A 34-year-old male was found to have an eroded sella turcica during routine skull radiography for an unrelated Bell palsy. Subsequently, a history of waning libido and episodic galactorrhea over the preceding six years was obtained. Neurological examination was normal. He had no visual field abnormalities and there were no clinical stigmata of endocrine dysfunction.

Investigations

The serum prolactin level was markedly elevated at 11,075 µg/L (normal range 0 to 25 µg/L). Computerized tomographic (CT) studies and magnetic resonance imaging (MRI) revealed a large pituitary tumor with suprasellar extension, base of skull destruction and bilateral cavernous sinus invasion. In addition, the tumor was invading the sphenoid sinus through a defect in the floor of the right side of the sella turcica (Figures 1, 2, 3).

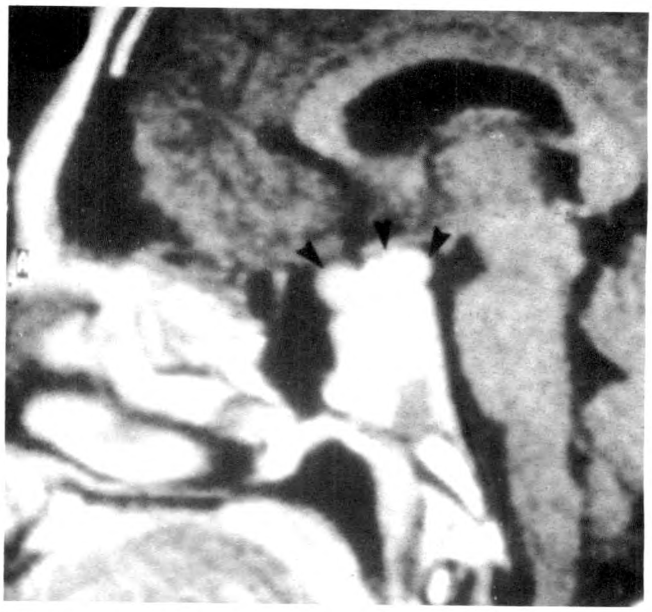

FIGURE 1. MRI in sagittal plane showing a large pituitary tumor with marked suprasellar extension (arrows outline upper border of tumor).

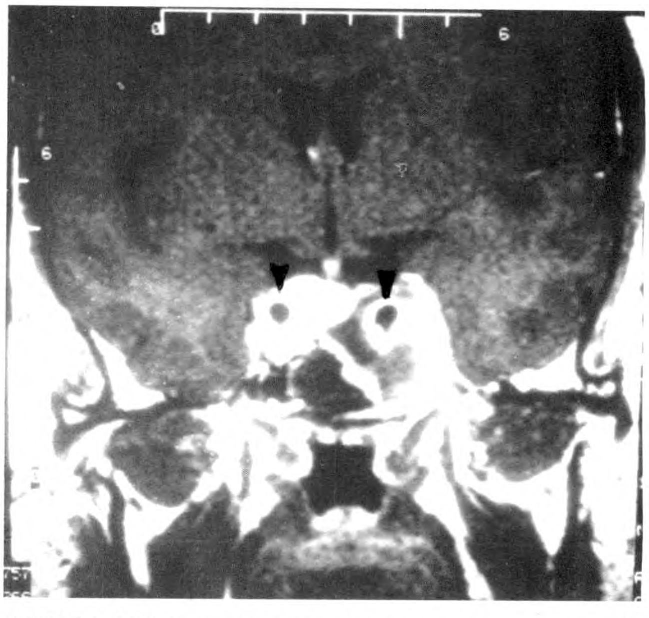

FIGURE 2. MRI in coronal plane showing tumor invasion of each cavernous sinus with encasement of the carotid arteries (arrows).

From the Division of Neurosurgery, (Drs. Russell, Al-Fayez, Joaquin), and Department of Medicine (Dr. Al-Rajeh, Abu Bakhr), King Fahad National Guard Hospital, Riyadh.

Address reprint requests and correspondence to Dr. Russell: King Fahad National Guard Hospital, P.O. Box 22490, Riyadh 11426, Saudi Arabia.

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TABLE : *Summary of 16 cases of CSF rhinorrhea occurring during bromocriptine treatment of pituitary tumor.*

Case	Author (Year)	Ref [ ]	Age	Sex	Radiological Features	Prolactin Level Pre-Tx (µg/L)	Prolactin Level Post-Tx (µg/L)	Interval to CSF Leak (Wks)	Other Treatment
1	Aronoff et al 1979	[4]	38	F	Enlarged sella. No SSE.	5,900	127	4	TSS
2	Afshar & Thomas 1982	[8]	28	F	Enlarged sella with eroded floor.	6,000	NR	1	None
3	Baskin & Wilson 1982	[5]	35	F	Initially a 6mm adenoma. Recurred after surgery with SSE	76.6	51	1	TSS (2) RT
4	Baskin & Wilson 1982	[5]	27	F	Large sellar mass. SSE	1,920	8	8	TSS RT
5	Landolt 1982	[7]	39	M	Sellar mass. SSE. Base of skull invasion	23,000	128	20	TSS RT
6	Landolt 1982	[7]	60	M	Sellar mass. SSE. Base of skull invasion	3,120	40	12	TSS RT
7	Landolt 1982	[7]	33	M	Sellar mass. SSE. Base of skull invasion	24,500	44	16	RT
8	Wilson et al 1983	[12]	32	F	Sellar mass. SSE and PSE "ballooning" into sphenoid sinus.	> 200 Exact level unknown	376	5	None
9	Wilson et al 1983	[12]	50	M	Sellar mass. PSE and extension downwards.	454	266	6	None
10	Holness et al 1984	[10]	38	M	Sellar mass. SSE Base of skull invasion	3,535	126	2	None
11	Kok et al 1985	[11]	47	M	Sellar mass. SSE. Invasion into sphenoidal sinus	13,500	640	32	None
12	Bronstein et al 1989	[9]	52	F	Sellar mass. SSE	1,110	168	64	None
13	Bronstein et al 1989	[9]	33	M	Sellar mass. SSE. Base of skull invasion	1,700	NR	68	None.
14	Hildebrand et al 1989	[6]	43	F	Sellar tumor. Base of skull invasion. Extended into nasopharynx	2,200	200	6	Transnasal biopsy
15	Hildebrand et al 1989	[6]	28	M	Sellar mass. Base of skull invasion	6,650	333	24	TCS
16	Russell et al (present case)		35	M	Sellar mass. SSE. Base of skull invasion	11,075	300	2	None

SSE=suprasellar extension; PSE=parasellar extension; TSS=transsphenoidal surgery; TCS=transcranial surgery; RT=radiotherapy; CSF=cerebrospinal fluid; Tx=treatment.

Treatment

Bromocriptine 2.5 mg three times daily was given. Three weeks later he developed profuse continuous discharge of clear watery fluid from the left nostril. This was not analyzed since it was considered unlikely to be anything but CSF. The serum prolactin level had fallen to 500 µg/L. Repeat CT scan showed a considerable reduction in overall tumor size with a dramatic shrinkage of the portion into the sphenoid sinus (Figure 4). A transsphenoidal exploration was carried out. CSF was found to be dripping from the left side of the sella turcica where the floor had been destroyed. Repair was carried out using subcutaneous fat and nasal cartilage. Tissue removed at surgery confirmed the diagnosis of a prolactinoma (electron-microscopic studies). Bromocriptine therapy was continued. Forty days after surgery, the CSF leak recurred. At this time the serum prolactin was less than 300 µg/L and MRI showed further tumor shrinkage. Another transsphenoidal exploration was performed. The erosion in the floor of the sella turcica was sealed with fascia lata, fibrin glue and a plug of methylmethacrylate. Three years later he is continuing bromocriptine treatment and is asymptomatic.

Analysis of Table

The details of 16 cases are summarized in the Table. There were seven females and nine males. The age ranged from 18 to 60 years (average 38). The patients presented with varying combinations of headache, endocrine dysfunction, and visual field abnormalities and these are not summarized. Pretreatment prolactin levels ranged from 76.6 to 24,500 µg/L (average 6558). Posttreatment levels in 15 patients ranged from 8 to 640 µg/L (average 167). In one case, the posttreatment level is not recorded.[8] CT or MRI studies showed the pituitary tumor and enlarged sella in all cases. In two, there was no extrasellar extension.[4,8] All others had extrasellar extension, usually with invasion of the base of the skull and cavernous

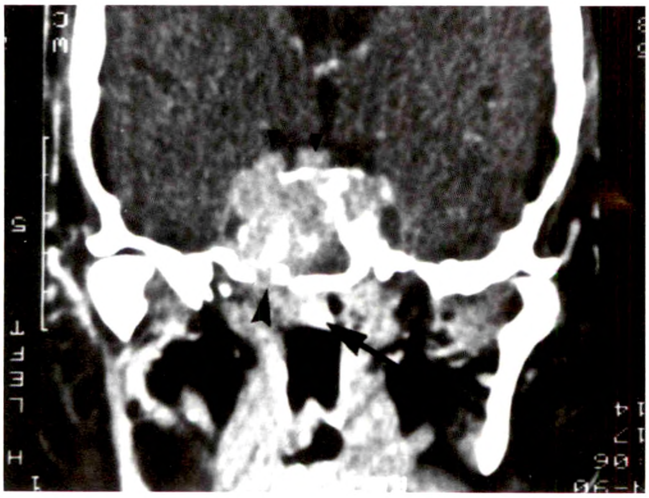

FIGURE 3. CT scan in coronal plane showing a defect in the floor of the sella turcica (medium size arrow) with tumor extending into the sphenoidal sinus (large arrow). (Smaller arrows outline upper border of tumor.)

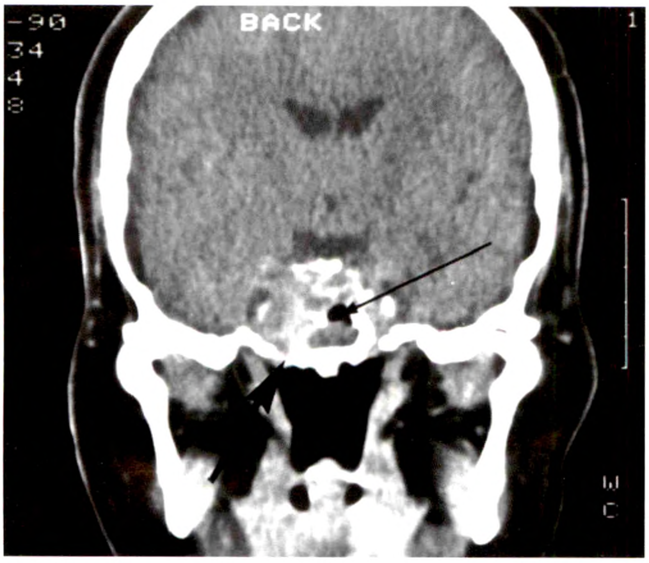

FIGURE 4. CT scan in coronal plane after administration of bromocriptine. The overall size of the tumor has decreased. Air is present within the sella turcica (thin arrow) and the tumor invading the sphenoid sinus has shrunk markedly so that only a fragment is seen within the sella floor defect (thick arrow).

sinus. In addition to ours, seven cases had only bromocriptine treatment before the CSF leak developed.[8-12] Eight cases had additional forms of treatment; one had transsphenoidal surgery,[4] four had transsphenoidal surgery plus radiotherapy,[5,7] one had radiotherapy,[7] one had transcranial surgery[6] and one had transnasal biopsy of the tumor.[13] However, none of these had CSF rhinorrhea until the addition of bromocriptine to the treatment. The time of occurrence of CSF rhinorrhea following bromocriptine treatment ranged from two to 68 weeks (average 14). In one case, the CSF leak ceased when bromocriptine was withdrawn, but recurred when it was restarted.[11] In seven cases as well as ours, the pathological studies confirmed the tumor to be a prolactinoma.[5,7,10,11] Three were chromophobe adenomas.[6,12] Two were reported as "pituitary adenoma".[4,9] In two, the pathology is not recorded[4,6] and in one, only necrotic tissue was obtained.[8] In 14 cases, the leak was repaired by the transsphenoidal route. Two had transcranial repair.[7,10] Our patient and one other[9] required a second operation because of recurrent CSF leak.

Discussion

Bromocriptine, a dopamine agonist, was first introduced in 1971, to treat hyperprolactinemia and restore fertility in patients with pituitary adenomas. It reduces tumor size by inhibiting hormone synthesis and causing involution of the prolactin producing cells, properties that have led to its widespread use.[13] Invasive pituitary adenomas cause destruction of the sellar floor and adjacent skull base. In such cases the tumor often herniates into the bone defect and acts as a "plug", preventing CSF leak.[4,7,12] Partial or total removal of tumor may cause CSF leakage by "unplugging" the defect, as can shrinkage of the tumor by radiotherapy. Since bromocriptine also diminishes tumor size, it may have a similar effect (Figure 4). Thus, CSF rhinorrhea due to the "unplugging" phenomenon may result from any treatment that reduces tumor size when bone destruction is present.[7,10,11]

Surgical treatment of CSF rhinorrhea in the presence of invasive pituitary tumors is difficult since the tumor is extensive and all of it cannot be removed. The transsphenoidal route is the preferred one for repair. It provides direct access to the tumor via the sella floor. In addition, a firm bed can be created for a graft, and this may prove useful if a subsequent transcranial approach becomes necessary.[12] At the second operation, we supplemented our fascia lata and fibrin glue repair with methylmethacrylate because of the extensive bone destruction. Although the use of foreign materials in this situation may increase the risk of infection and is not generally recommended, it proved useful in our patient and had no untoward effect.

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TWIN PREGNANCY WITH ACUTE MYELOBLASTIC LEUKEMIA: SUCCESSFUL OBSTETRIC AND HEMATOLOGICAL OUTCOME

Soad Al-Bahar, MRCPath; Ramesh Pandita, MD

The occurrence of acute leukemia during pregnancy is rare and acute myeloblastic leukemia complicates less than one of 75,000 pregnancies;[1] however, successful management of both remains a major therapeutic challenge.

There has been much concern about the short-term and long-term ill effects of chemotherapeutic agents used in pregnant patients on the fetus. Retrospective studies have failed to confirm adverse effects on the offspring of patients treated with cytotoxic agents during the second and third trimesters of pregnancy.[2-7] We report a case of twin pregnancy associated with acute myeloblastic leukemia with successful obstetric and hematological outcome. We also report lack of chromosomal abnormalities attributable to *in vitro* chemotherapeutic exposure in the newborns.

Case Report

In October 1991G, a 25-year-old multigravida presented with progressive pallor, generalized weakness, and amenorrhea. There was no history of bleeding, fever, or weight loss. Examination revealed pallor, no mucocutaneous bleeding, gum hypertrophy or bone tenderness, no hepatosplenomegaly and a uterine fundal height of 24 weeks' gestation. Investigations revealed Hb 61 g/L, platelets 242x10^9/L, WBC 0.8x10^9/L with peripheral blood showing prolymphocytes 9%, monocytes 1%, lymphocytes 81%, and 9% blasts. Bone marrow examination revealed infiltration by 74% myeloblasts and monoblasts and some promonocytes cytochemically. The majority of the blasts were Sudan black B positive, while nonspecific esterase was positive in 25% cells, periodic-acid-Schiff's stain was weak, diffusely positive in some blasts, and a diagnosis of acute myeloblastic leukemia (FAB AML M4) was established. Cytogenetic studies revealed normal karyotype. Serum chemistry and coagulation profile were normal. Ultrasonography confirmed pregnancy. She was treated with combination chemotherapy consisting of daunorubicin 45 mg/m^2 intravenously on days 1, 3, and 5; cytosine arabinoside 100 mg/m^2 IV infusion over three hours on days 1 to 7; and 6-thioguanine 100 mg/m^2 p.o. on days 1 to 7. Therapy was attended by severe myelosuppression requiring multiple packed red cell and platelet transfusions and a febrile episode which responded to amikacin, piperacillin, and ceftazidime. She achieved complete hematological recovery on day 27 and complete remission was documented by bone marrow examination. On day 29, she was administered the second course of combination chemotherapy consisting of the same drugs as used for the remission induction and this was attended by severe myelosuppression and a febrile neutropenic episode that responded to appropriate therapy. She achieved complete hematological recovery and repeat sonography showed a 32 week pregnancy and fetal normalcy. Further chemotherapy was deferred. At 38 weeks' gestation, she delivered twins by vaginal route, a female weighing 2.3 kg and a male weighing 2.2 kg, with no physical abnormalities detected. She received two additional courses of intensified chemotherapy consisting of daunorubicin 45 mg/m^2 IV on days 1, 3, and 5; VP-16 (etoposide) 100 mg/m^2 IV infusion over one hour on days 1 to 5; cytosine arabinoside 150 mg IV infusion over three hours on days 1 to 7. She continues to be in first remission for the last 12 months. Follow-up of the babies showed normal growth and development. Cytogenetic studies at six months of age revealed normal karyotype in the female child and inverted chromosome 9 in the male child. Cytogenetic studies on the patient (mother) while in remission showed inverted chromosome 9, while the studies on the father were normal. A review of the cytogenetic studies performed at the time of diagnosis of acute leukemia in the mother revealed a rare metaphase showing inverted chromosome 9.

Discussion

The occurrence of acute myeloblastic leukemia during pregnancy poses a serious threat to the maternal and fetal well-being and the aim of therapy should be long-term survival of both mother and fetus. The incidence of acute myeloblastic leukemia complicating pregnancy has been reported to be less than one in 75,000 pregnancies,[1] while the occurrence of pregnancy during treatment of acute myeloblastic leukemia is rarer. Zanzu et al[5] have reported one case of pregnancy during treatment of acute myeloblastic leukemia. Dara et al[8] reported pregnancy in a

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From the Department of Hematology, Kuwait Cancer Control Center, Kuwait.

Address reprint requests and correspondence to Dr. Al-Bahar: Consultant Hematologist, P.O. Box 12391, Al-Shamia 71654, Kuwait.

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patient undergoing treatment for acute lymphoblastic leukemia. The association of pregnancy does not adversely affect the remission induction rates. Reynoso et al,[2] in a review, documented 77% complete remission rates in acute myeloid leukemia, figures similar to the complete remission rates achieved in the nonpregnant patients. Roy et al,[3] in a study of six patients, achieved a complete remission rate of 66%, a rate comparable to one achieved in nonpregnant patients treated with similar protocols; the more aggressive regimens were associated with better survival. Our patient, treated with an intensive combination chemotherapy in standard dosage, confirms this observation.

The use of cytotoxic agents during the first trimester of pregnancy is associated with higher incidence of malformation,[4] though some studies have not documented such an association.[5] In a report of 19 cases of hematological malignancies including three patients with acute leukemia, no physical malformations were seen in 19 children born and followed up three to 19 years after birth.[5] The use of cytotoxic therapy in the second and third trimesters of pregnancy have not been shown to induce fetal malformation.[2,3,5-7] In our patient, who had twin pregnancy, neither fetus showed any malformations. Juarez et al[6] have reported one case of twin pregnancy associated with leukemia; however, it was accompanied by premature labor and both fetuses were dead.

The long-term follow-up reported on children born to mothers treated with cytotoxic therapy during pregnancy have not revealed any long-term ill effects on growth and development and have not documented any chromosomal abnormalities.[5,7,9] One of the newborns in this report was cytogenetically normal while another showed an inversion of chromosome 9; a repeat cytogenetic study in the mother while in remission revealed a similar finding while the father's karyotype was normal. Though inverted chromosome 9 has been very rarely documented in acute myeloblastic leukemia as part of complex cytogenetic abnormalities,[10] in our cases in both the mother and one of the babies, it appears to be a constitutional abnormality and is not related to the cytotoxic exposure.

Intensive standard cytotoxic therapy is effective in inducing complete remission from acute myeloblastic leukemia in pregnant women without inducing any developmental and cytogenetic abnormalities in the fetus when treated during second and third trimesters and is, at present, the most effective treatment for such patients. The mode and timing of delivery should be individualized; however, from the literature and this case report, vaginal delivery would appear to be feasible if there are no other indications for cesarean section. In the first trimester when the chances of induction of teratogenesis by chemotherapeutic agents are maximal, rates of fetal deaths are high and the mean survival of patients of acute myeloblastic leukemia without treatment is less than three months.[1] The best policy at present would be to initiate combination chemotherapy for the acute myeloblastic leukemia and if the patient does not spontaneously abort, termination of pregnancy should be carried out as soon as the patient achieves a complete remission or as soon as the clinical status permits it.

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Letters to the Editor

The *Annals of Saudi Medicine* welcomes *Letters to the Editor* from its readers. They may be on any topic, though the Editor especially encourages discussion of papers published in the *Annals*. Letters should be no more than 100 typewritten lines in length, typed double space, and submitted in triplicate. Letters may include one figure or brief table and up to five references. Submission of a letter constitutes permission for the *Annals* to use it for publication. Letters should not duplicate similar material being submitted or published elsewhere, and the *Annals* reserves the right to edit letters submitted. Letters referring to a recent *Annals* article should be received within six weeks of the article's publication.

Congenital Genu Recurvatum: A Report of Two Cases With Unusual Presentations

To the Editor: Congenital genu recurvatum is a rare entity in the newborn characterized by anterior hyperextension of the knee joint, prominence of femoral condyles in popliteal fossa, and increased transverse skin folds over the anterior surface of the knee.[1] Depending on the degree of severity, it can be further classified into three types: 1) congenital hyperextension; 2) congenital hyperextension with anterior subluxation of the tibia on the femur; and 3) congenital hyperextension with anterior dislocation of the tibia on the femur.[2] Most cases involving congenital genu recurvatum have been reported with unilateral involvement of the left leg in females with breech presentation in Negroes.[3] During the last seven years, we came across only two such cases with some unusual presentations. Rarity of such cases and the presence of uncommon features prompted us to report our findings.

Case 1 - This full term Saudi female was delivered to a G4 P3 mother by normal vaginal delivery. All other children were normal. Apgar score was 9 at one minute. Anthropometric measurements were within normal limits. The abnormality of both knee joints was noted soon after birth. Examination of the left knee revealed hyperextension of the left knee joint. The angulation was about 40° with prominence of the skin creases over the anterior aspect of the knee. This deformity was not easily reducible and the patella was not palpable. The upper end of the tibia was more prominent anteriorly and the lower end of the femur was prominent in the popliteal fossa. On passive reduction, no audible click was present. The right knee joint was also hyperextensible passively about 10° to 20° but there were no excessive movements at the articular surfaces to suggest subluxation or dislocation. There were no other associated congenital anomalies. Radiological examination of the left knee showed 40° of negative angulation at the tibiofemoral angle on lateral view with mild incongruity of the joint surfaces, suggestive of subluxation (Type 2 deformity). X-ray of the right knee showed 20° of negative angulation with congruity of the joint surfaces, suggestive of hyperextension only (Type 1 deformity). A serial above-knee corrective cast was applied following manipulations on the left side, while on the right side only passive manipulations were demonstrated to the mother. The patient was followed regularly in the Outpatient Department and recovered completely in three weeks.

Case 2 - This full term Saudi male was delivered to a G6 P5 mother by normal vaginal delivery. All other children were normal. Anthropometric measurements were within normal limits. Abnormality of the left knee joint was noted soon after birth. On examination, there was hyperextension of the left knee with angulation of about 50°. Skin creases were prominent on the anterior aspect of the knee joint. The patella was palpable and normal. There was contracture and atrophy of the quadriceps muscle on the left side. On passive flexion of the left knee joint, the joint was reducible with an audible click. The joint was redislocatable on hyperextension with anterior and lateral movement of the tibia. Radiological examination of the left knee joint showed 45° of negative tibiofemoral angulation on lateral view. The tibia was dislocated and displaced anteriorly, suggestive of dislocation (Type 3 deformity). The right knee joint was normal clinically and radiologically. There were no other associated congenital anomalies. A serial corrective cast was applied following weekly manipulations. After four weeks, the patient recovered completely and is doing well.

Various theories[3] were established for the etiology of this deformity: a) genetic; b) intrauterine traumatic developmental defects; c) mesenchymal defects; d) endocrine disorders; and e) teratogenic drugs or agents taken during pregnancy. The disease may be caused by degeneration of quadriceps muscles *in utero.* It may be associated with other congenital anomalies such as congenital dislocation of the hip, club foot, spina bifida, angiomata, strabismus, and absence of the patella.[3] No obvious reasons could be ascertained in our first case, although intrauterine traumatic developmental defects cannot be ruled out; while in the second case, contracture and atrophy of the quadriceps muscle was the possible reason.

Usually conservative treatment consists in repeated manipulations and castings to permit gradual flexion. Subcutaneous tenotomy of the iliotibial band is often necessary. In severe resistant cases, surgical intervention involves lengthening or sectioning of the quadriceps tendon, iliotibial band, anterior capsule and the posterior cruciate ligament.[4,5] Fortunately, both patients responded very well to conservative treatment in the form of repeated manipulations and castings.

Both patients described here had clinical features of the various types of the congenital genu recurvatum. In contrast to the previous reports, our babies were Saudi and delivered by vertex presentation. The male had unilateral involvement while the female had bilateral involvement. What we have presented is not commonly reported.

Vinay Joshi, MD
Department of Orthopedics
Sunil Kumar Rathi, MD
Abdelhay Elzubeir Eltahir, DTCH(UK) (Liverpool UK)
Department of Pediatrics
Zulfi General Hospital
Riyadh 11932, Saudi Arabia

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Serum Antibodies to Hepatitis C Virus in Turkish Patients With Chronic Liver Diseases

To the Editor: In Turkey, hepatitis B virus (HBV) has been found to be the main etiologic agent of chronic liver diseases.[1,2] In the present study, we investigated HBV, hepatitis C virus (HCV), and hepatitis D virus (HDV) status in patients with chronic liver diseases seen during the period from 1990G to 1992G. Excluded in this study were drug addicts, hemophiliacs, alcoholics, and patients with an autoimmune disease, primary biliary cirrhosis, drug hepatotoxicity, hepatocellular carcinoma, and metabolic disorders. HCV antibody (anti-HCV) was detected by second generation enzyme-linked immunosorbent assay (ELISA) (Abbott Laboratories). The positive results were confirmed by recombinant immunoblot assay (RIBA II) (Ortho Diagnostic). Histologic diagnosis was obtained in all patients with chronic hepatitis and 74 patients (90.2%) with cirrhosis. In the remaining patients (9.8%) with cirrhosis, biopsy was contraindicated or refused. The results were compared using the chi-square test with Yate's correction and Student's t-test as appropriate.

There were 126 male and 64 female patients with a mean age of 42.3 years (range 17 to 70 years). Of the 190 patients, 68 (35.7%) had evidence of HCV infection, a level higher than the percentage of 0.3% reported for blood donors in Turkey.[3] The prevalence found in our study was lower than the frequency of 63.6% found among Saudi patients with chronic liver diseases[4] and similar to the prevalence of 38.9% reported by Gessoni and Manoni.[5] One explanation for our lower prevalence may be the use of the second generation ELISA and confirming the positive results by RIBA 2. A false-positive reaction may have occurred in the first generation anti-HCV test. Second, this discrepancy may be due to the higher prevalence of HCV infection and/or lower prevalence of HBV infection among Saudi patients. In our study, 108 patients (56.8%) were positive only for hepatitis B surface antigen (HBsAg) and 15 (7.8%) patients had both HBsAg and anti-HCV in their serum. Of the 123 HBsAg positive patients, 35 (28.4%) were positive for anti-HDV. Fourteen patients were negative for markers of both HCV and HBV infections. The comparison of patients who were anti-HCV negative versus those who were positive is summarized in the Table. There were no differences in respect to age, sex, or frequency of abnormal alanine aminotransferase (ALT) ($P<0.05$), well in accordance with the Ayoola et al[4] series. A history of known parenteral exposure was found to be more frequent among anti-HCV positives (64.7%) versus anti-HCV negatives (13.9%, $P<0.0001$). Ayoola et al[4] only compared the history of blood transfusion and found that prior exposure to blood accounted for about one-third of HCV infections. The higher frequency in our study may be due to the involvement of patients with a history of surgery without transfusion. A history of hepatitis episode was more frequent among anti-HCV negatives (23.7%) than among anti-HCV positives (5.8%, $P=0.0018$).

Liver histology showed chronic persistent hepatitis (CPH) in 31 patients (16.3%), and chronic active hepatitis (CAH) in 77 (40.6%). Cirrhosis was diagnosed in 82 patients (43.1%). In eight patients, diagnosis was based on the presence of esophageal or gastroesophageal varices

TABLE : *Comparison of anti-positive and negative patients.*

	Anti-HCV positive		Anti-HCV negative		*P* value
Number of patients	68		122		
Male/Female	39/29		87/35		NS
Age (years)	44.3	(18-65)	41.1	(17-70)	NS
History of hepatitis	4	(5.8%)	29	(23.7%)	0.0018
Previous surgery/ blood transfusion	44	(64.7%)	17	(13.9%)	<0.0001
Elevated ALT (1.5 x normal)	30	(44.1%)	45	(36.8%)	NS
HBsAg	15	(22.0%)	108	(88.5%)	<0.001
Anti-HCV	32	(47.0%)	96	(78.6%)	<0.001
HDV	2	(2.9%)	33	(27.0%)	<0.001
CPH	12	(17.6%)	19	(15.5%)	NS
CAH	35	(51.4%)	42	(34.4%)	0.0218
Cirrhosis	21	(30.8%)	61	(50.0%)	0.0108

ALT=alanine aminotransferase; HBsAg=hepatitis B surface antigen; HDV=hepatitis D virus; CPH=chronic persistent hepatitis; CAH=chronic active hepatitis; NS=not significant.

ultrasonographic findings of portal hypertension, splenomegaly, and ascites. In contrast to the lack of difference in the anti-HCV prevalence in groups in relationship to histology in Ayoola et al[4] series, we found that chronic active hepatitis was more frequent among anti-HCV positives (P=0.0218) and cirrhosis was more prevalent among anti-HCV negatives (P=0.0108).

From our data, it is evident that HBV is the main agent responsible for adult chronic liver diseases in Turkey and anti-HCV should be tested in patients, especially where the etiology is unknown.

Esin Özyilkan, MD
Gonca Tatar, MD
Tankut Köseoglu, MD
Hasan Telatar, MD
Hacettepe University Faculty of Medicine
Department of Internal Medicine
Division of Gastroenterology
Ankara, Turkey

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Electroencephalographic (EEG) Periodic Lateralized Discharges (PLEDs) from Cerebral Infarction in an Unstressed Full Term Newborn?

To the Editor: Singh et al[1] presents what is probably the first case of periodic lateralized discharges (PLEDs) in an unstressed full term newborn with stroke, documented by an electroencephalographic (EEG) sample (Figure 2 of 1). Unfortunately, this figure is small, poorly reproduced, and lacks time and amplitude scales. It is not stated whether the child slept or was awake, and physiological variables other than EEG to establish this were not recorded.

Although the high regular, very sharp discharges generally are left-sided in distribution, a more detailed analysis shows phase reversal between Fp1-T3 (channel 3) and T3-O1 (channel 4), and locates them to the T3 (left mid temporal) electrode. The polarity of the discharges at Cz-C3 (channel 11) indicates that C3 is also active. However, this is at variance with absent discharges at Fp1-C3 (channel 7), C3-O1 (channel 8), and C3-T3 (channel 12). It further perturbs that the C3-T3 (left centro-temporal) slow wave activity seems to phase reverse with that of the right occipital region. Could the montage be erroneous?

Though this might represent left temporo-central PLEDs, better documentation with comments addressing the above discrepancies would be needed to suggest that they are more than artifacts.

Bent Stigsby, MD, PhD
Medical Director, Neurophysiology Laboratory
Consultant Clinical Neurophysiologist
Department of Medicine (MBC-46)
King Faisal Specialist Hospital
and Research Centre
P.O. Box 3354
Riyadh 11211, Saudi Arabia

Reference

1. Singh P, Singh B, Khan M. Focal seizures, a manifestation of stroke in an unstressed full term neonate. Ann Saudi Med 1993;13(2):187-9.

Reply

To the Editor: We agree with Dr. Stigsby that the electroencephalographic (EEG) figure is small (size decided by Editorial Board - Information for Authors), poorly reproduced, lacks time and amplitude correlate and that the child's state of alertness was not mentioned. While all of these points are important, they do not affect the diagnosis of periodic lateralized discharges (PLEDs) in this patient in any way. As the main purpose of the article was to report the association of focal seizures in neonates with stroke, we do not disagree with the editors in saving space by reducing the size of the EEG figure. This EEG certainly does not fulfill all the physical and mathematical criteria of an electrical dipole situated near the surface of an ideal spherical conductor. However, unlike an ideal spherical conductor obliquely situated, electrical fields inside the skull of a baby may not show symmetrical phase reversal in all directions. We are convinced that, in spite of a few minor discrepancies, a periodic spike focus seen at two adjacent electrodes overlying an acute stroke is unlikely to be an artifact and can be safely classified as PLEDs.

Poonam Singh, MD
Balbir Singh, MD
Masood Khan, MD
Riyadh Armed Forces Hospital
Department of Pediatrics
P.O. Box 7897
Riyadh 11159, Saudi Arabia.

Dermatitis Artifacta in a Saudi Female

To the Editor: Dermatitis artifacta consists of self-inflicted lesions. It is extremely important to be aware of this entity in order to avoid unnecessary investigations and perhaps surgical intervention. In this communication, a case of dermatitis artifacta involving the breast of a female is presented. It appears to be the first case reported from the Kingdom of Saudi Arabia.

A 30-year-old Saudi female was admitted to King Fahd Hospital at Al Baha for the evaluation of a skin lesion on the left breast. It was of four months' duration, asymptomatic and persistent. The patient appeared indifferent about the lesion and was unwilling to discuss its early stages of development. She denied any contact of the breast with chemicals of traumatizing means. She was married and had four children, but had not seen her husband for the past four years, although they remained legally married. She and her children were living in her parents' home. Examination revealed a superficially ulcerated, oozy and bizarre-shaped lesion on the frontal surface of the left breast. The areola and nipple were clear. The lesion was about 7 cm and 5 cm at its longest diameters and was not indurated or tender. No underlying mass was detected. The remaining skin including the other breast was normal and no abnormality was found on systemic examination. A clinical diagnosis of dermatitis artifacta was considered and a biopsy from the lesion showed an eczematous type of cutaneous reaction with no evidence of malignancy. The diseased area was occluded with dry surgical gauze. She was not confronted directly with the diagnosis, but instead with sympathy and understanding, the nature of her illness was conveyed to her. A week later the lesion began healing and a follow-up at two weeks showed only postinflammatory hyperpigmentation and no new lesions.

Dermatitis artifacta, also known as dermatitis factitia, affects females more commonly than males and the incidence is highest in young adults and teenagers.[1] Most of the patients have a personality disorder.[2] A variety of stresses act as precipitating factors for the self induction of cutaneous lesions that often serve as a cry for help from these patients.[3,4] Artifactual lesions are also seen in psychotics and produced deliberately by malingerers for material gain, e.g., compensation, money, or avoidance of duties. In the case presented here, the patient did not manifest psychotic features and had no obvious gain from her lesion. Rather, her unnaturally disarrayed marital state seemed to be a significant etiologic factor and she might have inflicted the lesion to draw attention to it. The patients usually deny that they are inducing the lesions, as was the case in this patient, unless they are psychotic and the lesions are part of a hallucinatory or delusional expression.[5] It is not definite whether these patients are fully conscious of the self-infliction of lesions.[6] Also, they lack concern about the lesions and have no wish to become well.[6,7]

Morphologically, the lesions are bizarre in shape. Ulceration, deep excoriations, erythema, bullae, bruises, superficial gangrene and induration may be seen, depending on the means used by the patients to damage the skin. These include burning, scarification with sharp tools, application and injection of chemicals, squeezing the skin and scratching with fingernails. The means used by the patient in the case presented here were not clearly known but the oozy clinical appearance of the lesion and its dermatitis type of reaction in the histopathology suggest an eczematous response to contact with a chemical. The lesions are produced on areas accessible to the patient's dominant hand, as seen in this case. They, unlike those of genuine skin diseases, do not evolve from early stages but rather appear suddenly and fully developed. Scars or pigmentary changes indicating past lesions may be present along with fresh ones.

Dermatitis artifacta sometimes is difficult to diagnose and the physician's fear of overlooking an organic disease makes the diagnosis even more difficult. Suspicion should be aroused by the vague history that was cited as hollow;[7] a clear impression of how the lesions developed is impossible to obtain from the patients and by the bizarre-looking lesions that are not consistent with any known dermatosis. The patient's indifference to the lesions and stressful life situation are also diagnostic pointers. Sometimes it may be necessary to confirm the diagnosis by occluding the affected area and observing the patient closely in a hospital. Occlusive dressings may deny the patient's ready access to the affected area and permit healing but on the unoccluded skin, new lesions may be induced.[7] Occurrence of new lesions under the dressing should not always be considered against the diagnosis of dermatitis artifacta because instances of patients injecting irritants through occlusive dressings have been cited.[7] Close observation deprives the patients from the privacy and means required for the infliction of lesions but they may become restless and tense.

Directly confronting the patient with the artifactual nature of the lesions should be avoided because it can result in unpleasant scenes of angry denial.[3,7] Likewise, a recommendation for psychiatric referral may be rejected immediately and the patient may opt to transfer to another physician to look for treatment. Rather, it is important to understand the emotional state and living circumstances of the patient and maintain a nonjudgmental attitude and close relationship with the patient.[4] This will enable the physician to win the patient's trust and indirectly convey to her or him the artifactual nature of the lesions.[3,7] For some patients, especially those who are psychologically relatively healthy, this supportive therapy may be all that is required and they may recover and allow their lesions to heal,[5] as it was in the case presented here. Appropriate manipulation of the living environment is to be encouraged for those patients who are found to be intolerant to their external pressure.[3] In severe or persistent cases, expert and sympathetic psychiatric treatment is required and may be administered on a collaborative basis with the attending dermatologist.

Salih H. M. Al-Jabre, MBBS, MSc, PhD
Assistant Professor, Department of Dermatology
King Faisal University, Dammam
King Fahd Hospital of the University, Al Khobar
P.O. Box 1746
Dammam 31441, Saudi Arabia

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Book Reviews

Rockwood and Green's Fractures in Adults

by Charles A. Rockwood, Jr., David P. Green,
Robert W. Bucholz; with 49 contributors
J. B. Lippincott Company, Philadelphia, PA, USA
3rd Edition, 1991
US $359
ISBN: 0-397-50975-8 (set:v.1,2, and 3)
ISBN: 0-397-51151-5 (set:v.1 and 2)
ISBN: 0-397-51230-9 (v.1)

This is the 3rd Edition of this textbook on fracture management, first published in 1975G. For the past 15 years, it has been the main reference for orthopedic surgeons throughout the world in the management of fractures and dislocations. In 1984G, the textbook was expanded and modified to go along with the rapidly changing technology in implants and fixation techniques.

This third edition continues with the same format of the previous two editions, with sections on nonoperative treatment as well as the current accepted standards in operative reduction. There have been major additions in the management of lower extremity fractures, especially in regard to the operative treatment of open fractures.

There has been extensive rewriting of some of the chapters, many of these by new authors. The format of presenting the nonoperative, operative and authors' preferred method of treatment is unchanged. This textbook remains the most complete, up-to-date textbook in fracture management available today. As fracture care has evolved considerably over the last several years, so has this textbook. It should be in the library of any surgeon who is involved with trauma care.

Paul G. Moreau, MD
Deputy Chairman and Consultant
Department of Orthopedics (MBC-77)
King Faisal Specialist Hospital
and Research Centre
P.O. Box 3354,
Riyadh 11211, Saudi Arabia

Textbook of Internal Medicine, Vol. 1

by William Kelley
J. B. Lippincott Company, Philadelphia ,PA, USA
2nd Edition, 1992
US $99
ISBN: 0-397-51048-9

The first edition of Kelley's Textbook of Internal Medicine was published in 1989 and enthusiastically received. It was selected Outstanding Medical Clinical Book of 1989 by the Association of the American Publishers, and has already been translated into Spanish. In this second edition all 524 chapters are updated and 20% of the content is entirely rewritten. The gap between European and North American medicine has narrowed considerably over the past 10 to 15 years and the reviewer, who has not trained in North America, found no idiosyncratic opinions expressed.

The editors have set themselves the highest goals possible; they want the textbook to become the best available throughout the world, to be an encyclopedic reference source, as well as a daily guide to patient care and for the text to be current, comprehensive and clearly written. They have succeeded. Where Kelley's textbook is particularly unique is in its structure of each of the ten clinical parts covering different subspecialties. Each part is divided into three sections. The first section gives the scientific basis of the subspecialty with a general description of pathophysiology and biochemical mechanisms. The second section contains comprehensive descriptions of separate disorders within the subspecialty and the third details approaches to patients according to their mode of presentation, concentrating on differential diagnoses, investigations, their sensitivity and specificity and management of the different disorders. This subdivision makes it easy for medical students, residents in training, as well as senior practitioners to quickly find useful information. Medical students and junior residents will concentrate mainly on the first two sections, and more senior practitioners particularly on the third.

The book is written in a clear instructive language, the typography and layout are inviting and the content very current. This comprehensive Textbook of Internal Medicine, therefore, not only competes with Harrison and Cecil's classical texts, but also with the monthly updated Scientific American Medicine and very successfully so.

The text has a fresh appearance, perhaps because most of the contributors, who have nearly all contributed seminar papers in their field, have never before written textbook chapters. A very useful detail is the appearance of a cross reference system at the end of many chapters, directing the reader to other parts of the textbook containing material linked to the subject in question. This feature significantly enhances and eases the use of the textbook as a tool.

The textbook's first part has some unique and interesting chapters on, for example, clinical ethics, humanistic qualities in Medicine, the periodic health evaluation, rehabilitation and principles of diagnostic testing. The last part is exclusively dedictated to three sections on Geriatric Medicine, dealing with all important aspects of major illnesses of the elderly.

The only disappointment is that the description of psychiatric illnesses is reduced to only four pages. This is a minor quibble considering the qualities of this textbook, which is of the highest standard, both in content, organization and presentation; in my opinion, the best buy among the large comprehensive textbooks in Internal Medicine for both students, trainees and senior practitioners.

Jens O. Sieck, FRCP
Head, Section of Internal Medicine
Department of Medicine (MBC-46)
King Faisal Specialist Hospital
and Research Centre
P.O. Box 3354,
Riyadh 11211, Saudi Arabia

Wolf-Heidegger's Atlas of Human Anatomy

by Hans Frick, Benno Kummer, Reinhard Putz
S. Karger, Basel
4th Edition, 1990
US $100
ISBN: 3-8055-4289-5

This is a mainly topographical atlas with a short introductory section on systemic anatomy. Each region is illustrated from the interior, starting usually with the skeleton and adding soft tissues, viscera, nerves, vessels, etc. The organization is logical and the area of interest is easily located, usually without resorting to the detailed (28pp) index.

The illustrations are clear and detailed. Most are drawings. Some CT scans and MR scans are incorporated for comparison. The nomenclature is the 6th Nomina Anatomica which may be a little unfamiliar for the physician with an anglosaxon training (A. gastrica sinistra for left gastric artery, plica vocalis for vocal cord, etc.)

The closest competitor to this atlas is Pernkopf's "Atlas of Topographical and Applied Anatomy". The latter has the advantage of a larger format, but it is in two volumes (with a separate index volume). The law of multi-volume work states that the desired information is always located in the other volume. Therefore, this atlas has the edge as far as quick and easy reference is concerned. I have tested it for some months in the Histopathology Laboratory when dissecting unfamiliar specimens and teaching residents. As fas as surgical pathology practice is concerned, it has proven excellent.

Bo Hainau, MD
Consultant, Anatomic Pathology
Department of Pathology (MBC-10)
King Faisal Specialist Hospital
and Research Centre
P.O. Box 3354,
Riyadh 11211, Saudi Arabia

ACKNOWLEDGMENTS

The Editorial Board of the *Annals of Saudi Medicine* would like to thank the following individuals who have reviewed articles for Volume 13, 1993.

Dr. A. Majeed Abdulkareem
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Mohamed Abo-Melha
Riyadh Armed Forces Hospital
Riyadh, Saudi Arabia

Prof. Hassan Abu-Aisha
College of Medicine
King Saud University
Riyadh, Saudi Arabia

Dr. Mohamed Abu-Ghosh
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Yousef Abu-Osba
The University of Jordan
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King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Prof. Babatunde Adelusi
College of Medicine
King Saud University
Riyadh, Saudi Arabia

Dr. Mohammed Al-Ahdal
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Mohamed Ahmed
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Saeed Ahmed
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Prof. E.O. Akande
World Health Organization
Geneva, Switzerland

Dr. Saleh Alaiyan
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Hatim Ali
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. M. Ashraf Ali
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Prof. Mohammed Al-Shabrawy Ali
College of Medicine
King Saud University
Riyadh, Saudi Arabia

Dr. Tarek Amin
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. John Antonius
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

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King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Mohamed Arafa
College of Medicine
King Saud University
Riyadh, Saudi Arabia

Dr. Abdulrahman Al-Arfaj
College of Medicine
King Saud University
Riyadh, Saudi Arabia

Dr. Mahmoud Ashour
College of Medicine
King Saud University
Riyadh, Saudi Arabia

Dr. Abdullah Al-Ashwal
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Abdul Karim Al-Aska
Security Forces Hospital
Riyadh, Saudi Arabia

Dr. Ahmad Abu El-Asrar
College of Medicine
King Saud University
Riyadh, Saudi Arabia

Dr. Alberto Ayala
MD Anderson Hospital
Houston, Texas, USA

Prof. Banji Ayoola
College of Medicine
King Saud University
Riyadh, Saudi Arabia

Dr. Asif Ayub
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Robby Bacchus
Riyadh Armed Forces Hospital
Riyadh, Saudi Arabia

Prof. Hassan Bahakim
College of Medicine
King Saud University
Riyadh, Saudi Arabia

Dr. Younes Bakri
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Hannaa Banjar
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

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King Fahad Hospital
Al Madina, Saudi Arabia

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King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Rahman Beg
King Fahad National Guard Hospital
Riyadh, Saudi Arabia

Dr. Patrick Belfrage
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Stener Bernvil
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Saeed Bohlega
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Abderrezak Bouchama
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Daniel Booser
MD Anderson Hospital
Houston, Texas, USA

Dr. Gudrun Brismar
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Jan Brismar
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. J.M.H. Buckler
University of Leeds
Leeds, England

Dr. Terrance Calloway
King Fahad National Guard Hospital
Riyadh, Saudi Arabia

Dr. Kutaiba Chaleby
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Amir Channa
College of Medicine
King Saud University
Riyadh, Saudi Arabia

Dr. Siser Chattopadhyay
Maternity & Children's Hospital
Riyadh, Saudi Arabia

Dr. Abdul Rasheed Choudhury
Riyadh Armed Forces Hospital
Riyadh, Saudi Arabia

Dr. M.N.H. Chowdhury
College of Medicine
King Saud University
Riyadh, Saudi Arabia

Dr. Ivan Christophersen
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Timothy Cleary
University of Miami
Miami, Florida, USA

Dr. Hugh Clink
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Robert Coates
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Theodore Cooke
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Larry Copeland
Ohio State University
College of Medicine
Columbus, Ohio, USA

Dr. Jean Cronstedt
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Nabil Dahmash
College of Medicine
King Saud University
Riyadh, Saudi Arabia

Dr. Abdullah Al-Dalaan
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Saleh Al-Deeb
Riyadh Armed Forces Hospital
Riyadh, Saudi Arabia

Dr. Jean Paul Dery
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Edward De Vol
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. William Doyle
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Ross Duncan
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Abdullah Eisa
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Michael Ellis
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Ronald Ellis
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Jad Elrab
College of Medicine
King Saud University
Riyadh, Saudi Arabia

Dr. Kamal Elramahi
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Bjorn Ericsson
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Peter Ernst
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Adnan Ezzat
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Faleh Z. Al-Faleh
College of Medicine
King Saud University
Riyadh, Saudi Arabia

Dr. Olufunscho O. Famuyiwa
College of Medicine
King Saud University
Riyadh, Saudi Arabia

Dr. Saad Al-Faqih
College of Medicine
King Saud University
Riyadh, Saudi Arabia

Dr. Gale Farid
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Zareen Farooqi
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Mohamed Fawzy
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Adam Finn
Children's Hospital
Sheffield, England

Dr. Robert E. Fontain
Ministry of Health
Riyadh, Saudi Arabia

Dr. Bagher Forghani
California State University
Department of Health Sciences
Berkeley, California, USA

Prof. Abdulrahman S. Al-Frayh
College of Medicine
King Saud University
Riyadh, Saudi Arabia

Dr. Husn Frayha
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Osman Furayh
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Ahmed Gad
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Prof. Abdel Galil M. Abdel Gader
College of Medicine
King Saud University
Riyadh, Saudi Arabia

Dr. Omar Galal
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Alexander Gallus
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Mammon Gammas
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Robert Ganelin
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Generoso Gascon
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Kaare Getz
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Nitya R. Ghagak
Medical College of Virginia
Richmond, Virginia, USA

Dr. Ronald Gillum
Oklahoma Memorial Hospital
Oklahoma City, Oklahoma, USA

Dr. Alex von Graevenitz
Institut fur Medizinische
Zurich, Switzerland

Dr. Viggo Graf-Lonnevig
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. David Graham
Baylor College of Medicine
Houston, Texas, USA

Dr. Brian Greenhill
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. William Greer
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Saad Haddab
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Saeed Hafiz
King Fahad National Guard Hospital
Riyadh, Saudi Arabia

Dr. Abdulrazzaq Haider
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Bo Hainau
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Mohammed Hajjaj
College of Medicine
King Saud University
Riyadh, Saudi Arabia

Dr. Sami Al-Hajjar
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Abdul Haleem
Riyadh Armed Forces Hospital
Riyadh, Saudi Arabia

Prof. R. Abdel Haleem
College of Medicine
King Saud University
Riyadh, Saudi Arabia

Dr. Magid Halim
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Mortada Halim
Riyadh Armed Forces Hospital
Riyadh, Saudi Arabia

Dr. Carolus Hamilton
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Prof. Khalid Haque
St. Helier Hospital
London, England

Dr. Anita Harding
Neurological Institute
London, England

Dr. Harb Harfi
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Ahmed Hassan
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Bassam Hawary
College of Medicine
King Saud University
Riyadh, Saudi Arabia

Prof. M.A.F. El-Hazmi
College of Medicine
King Saud University
Riyadh, Saudi Arabia

Dr. Mogbel Al-Hedaithy
College of Medicine
King Saud University
Riyadh, Saudi Arabia

Dr. Henry G. Herrod
University of Tennessee
Memphis, Tennessee, USA

Dr. Guillermo A. Herrera
University of Alabama
at Birmingham
Birmingham, Alabama, USA

Dr. Akram Hilali
King Fahad National Guard Hospital
Riyadh, Saudi Arabia

Dr. Peter Horowitz
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Mogbil Al-Hudaithy
College of Medicine
King Saud University
Riyadh, Saudi Arabia

Dr. Claes Hugosson
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

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College of Medicine
King Saud University
Riyadh, Saudi Arbia

Dr. Imtiaz Husain
College of Medicine
King Saud University
Riyadh, Saudi Arabia

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King Abdulaziz University
Jeddah, Saudi Arabia

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and Research Centre
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and Research Centre
Riyadh, Saudi Arabia

Dr. John MuirJackson
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

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King Saud University
Riyadh, Saudi Arabia

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and Research Centre
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King Saud University
Riyadh, Saudi Arabia

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Riyadh, Saudi Arabia

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Riyadh, Saudi Arabia

Dr. Abdul Hakiem Kattan
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and Research Centre
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and Research Centre
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Riyadh, Saudi Arabia

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Riyadh, Saudi Arabia

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King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

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Riyadh Armed Forces Hospital
Riyadh, Saudi Arabia

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College of Medicine
King Saud University
Riyadh, Saudi Arabia

Prof. Aize Kijlstra
Editor-In-Chief
Ocular Immunology and
Inflammation
Amsterdam, The Netherlands

Dr. Mohammed Naji Kordy
King Abdulaziz University
Jeddah, Saudi Arabia

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Riyadh Armed Forces Hospital
Riyadh, Saudi Arabia

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Riyadh, Saudi Arabia

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King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

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and Research Centre
Riyadh, Saudi Arabia

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College of Medicine
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Riyadh, Saudi Arabia

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and Research Centre
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and Research Centre
Riyadh, Saudi Arabia

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and Research Centre
Riyadh, Saudi Arabia

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and Research Centre
Riyadh, Saudi Arabia

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King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

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and Research Centre
Riyadh, Saudi Arabia

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King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Graham Miller
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

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College of Medicine at Peoria
Peoria, Illinois, USA

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King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

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College of Medicine
King Saud University at Abha
Abha, Saudi Arabia

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College of Medicine
King Saud University
Riyadh, Saudi Arabia

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Riyadh, Saudi Arabia

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King Saud University
Riyadh, Saudi Arabia

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College of Medicine
King Saud University
Riyadh, Saudi Arabia

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King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

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College of Medicine
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Riyadh, Saudi Arabia

Dr. Hamad Al-Muhaimeed
King Abdulaziz University Hospital
Riyadh, Saudi Arabia

Dr. Ahmad Mutwaili
Security Forces Hospital
Riyadh, Saudi Arabia

Dr. Abdalla Al-Nasser
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Abdulaziz Al-Nasser
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Ms. Marilyn Navia
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. S. Nawaz
Riyadh Armed Forces Hospital
Riyadh, Saudi Arabia

Dr. Hisham Nazer
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Michael Nester
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

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College of Medicine
King Saud University
Riyadh, Saudi Arabia

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University of California
San Francisco, California, USA

Dr. Shigeaki Ohno
Yokohama City University
Yokohama, Japan

Dr. S.O. Olusi
College of Medicine
King Saud University
Riyadh, Saudi Arabia

Dr. Ossama Osman
Mercer University
School of Medicine
Macon, Georgia, USA

Dr. Saud Al-Oufi
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Pinar Ozand
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Prof. C.P. Panayiotopoulos
St. Thomas' Hospital
London, England

Dr. Shirish Parikh
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

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King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

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King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Barry Posner
Royal Victoria Hospital
Montreal, Ontario, Canada

Dr. R.A. Primhak
Children's Hospital
Sheffield, England

Dr. S.M. Hussain Qadri
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Faisal Al-Qassim
College of Medicine
King Saud University
Riyadh, Saudi Arabia

Dr. Mohammed Al-Quaiz
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Wajeh Qunibi
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Abdallah Rabeeah
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Ziad Rafii
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Amjad Rahi
Ministry of Health
Dammam, Saudi Arabia

Dr. Bengt Rahm
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Feryal Rahman
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Sami Ramia
College of Medicine
King Saud University
Riyadh, Saudi Arabia

Dr. Abdel L. Rashad
Oregon Health Sciences University
Portland, Oregon, USA

Dr. Soud Al-Rasheed
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Rashed Al-Rashed
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Hassan Rayes
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Sethu Reddy
Halifax Infirmary
Halifax, Nova Scotia

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Veterans Affairs Medical Center
Salt Lake City, Utah, USA

Dr. Abdellatif Rejjal
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. David Rhydderch
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Ayman Rifai
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. William Riley
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Khalid Ali Al-Rubiaan
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Antoine Saber
Riyadh Armed Forces Hospital
Riyadh, Saudi Arabia

Dr. Kwesi Sackey
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

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King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

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King Fahad National Guard Hospital
Riyadh, Saudi Arabia

Dr. Nadia Sakati
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Iman Al-Saleh
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Thomas Salerno
University of Toronto
Toronto, Ontario, Canada

Prof. Asal I. Al-Samarrai
College of Medicine
King Saud University
Riyadh, Saudi Arabia

Dr. Khalid Sami
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Sami Sanjad
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. S.K. Sanyal
King Fahd Hospital of the University
Al-Khobar, Saudi Arabia

Dr. Jalal Saour
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Sayed A. Sattar
University of Ottawa
Ottawa, Ontario, Canada

Dr. Sultan Al-Sedairy
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Richard Seddon
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Amin Seraj
King Abdulaziz University Hospital
Riyadh, Saudi Arabia

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University of West Indies
Kingston, Jamaica

Dr. Khalid Shaibani
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Aftab Shaikh
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Souheil Shebib
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Kirtikant V. Sheth
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Atef Shibl
College of Pharmacy
King Saud University
Riyadh, Saudi Arabia

Dr. Mohammad Hisham Al-Sibai
College of Medicine
King Faisal University
Dammam, Saudi Arabia

Dr. Eugenius Siemkowicz
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Walther von Sinner
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Edir Siqueira
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. V. Siva
Security Forces Hospital
Riyadh, Saudi Arabia

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King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Nour Sneige
MD Anderson Hospital
Houston, Texas, USA

Dr. M.O. Al-Sohaibani
College of Medicine
King Saud University
Riyadh, Saudi Arabia

Dr. Hassan Solh
The Hospital for Sick Children
Toronto, Ontario, Canada

Dr. David Spence
King Faisal Specialist Hospital
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Riyadh, Saudi Arabia

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College of Medicine
King Saud University
Riyadh, Saudi Arabia

Dr. Miltiadis A. Stefadouros
King Fahad National Guard Hospital
Riyadh, Saudi Arabia

Dr. Robert Stewart
Cleveland Clinic Foundation
Cleveland, Ohio, USA

Dr. Bent Stigsby
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Dag Stokke
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Daniel P. Stites
University of California
San Francisco, California, USA

Dr. Raold Strandjord
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Paul Swan
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Iyad M. Subei
Erfan-Bagedo Hospital
Jeddah, Saudi Arabia

Dr. Riad Abbas Sulimani
College of Medicine
King Saud University
Riyadh, Saudi Arabia

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College of Medicine
King Saud University
Riyadh, Saudi Arabia

Dr. Torsten Sundin
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Khalid Taibah
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Padma Tipirneni
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Kevin K. Tu
Memorial Division
Charleston, West Virginia, USA

Dr. Mohammed Tufail
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Haysam Tufenkeji
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Guido Vanhaleweyk
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

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Children's Hospital
Sheffield, England

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University of Oklahoma
Health Sciences Center
Oklahoma City, Oklahoma, USA

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King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

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Baylor College of Medicine
Houston, Texas, USA

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King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

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King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

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Deutsches Herzzentrum Berlin
Berlin, Deutschland

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Riyadh, Saudi Arabia

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King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

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King Abdulaziz University Hospital
Riyadh, Saudi Arabia

Dr. Liaqat Zaman
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Dr. Ekram Zayed
King Faisal Specialist Hospital
and Research Centre
Riyadh, Saudi Arabia

Announcements

The *Annals of Saudi Medicine* is pleased to publish announcements of educational opportunities of interest to its readers. For adequate publication layout time for publicity, notices of postgraduate schedules, courses, meetings, and lectures must be received at least **six months prior** to the date of occurrence. Please send relevant information to Mary Anne Wrynn-De Santis, Senior Editor, *Annals of Saudi Medicine*, Publications Office (MBC-36), Academic Affairs & Postgraduate Education, King Faisal Specialist Hospital & Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia. Tel: 464-7272 extensions 1815/1816; Fax: (01) 442-7237.

King Faisal Hospital & Research Centre Academic Calendar for 1414H/1993-1994G

King Faisal Specialist Hospital & Research Centre has scheduled the following Academic Calendar for 1993-1994G/1414H:

Foreign Medical Graduates Examination in the Medical Sciences (FMGEMS)	23-24 Muharram 1414 13-14 July 1993
United States Medical Licensing Examination (USMLE) Step 2	22-23 Rabi Al-Awal 1414 8-9 September 1993
United States Medical Licensing Examination (USMLE) Step 1	5-6 Rabi Al-Thani 1414 21-22 September 1993
Symposium on Rheumatic Heart Disease	21-22 Jumada Al-Thani 1414 4-5 December 1993
United States Medical Licensing Examination (USMLE) Step 2	18-19 Shawwal 1414 30-31 March 1994
Symposium of Recent Advances in Obstetrics and Gynecology	24-25 Shawwal 1414 5-6 April 1994
Symposium of Emergency Medical Services in Saudi Arabia	8-9 Dhu Al-Qa'da 1414 19-20 April 1994
United States Medical Licensing Examination (USMLE) Step 1	29-30 Dhu Al-Hijjah 1414 8-9 June 1994

For further information, contact: Academic Affairs & Postgraduate Education (MBC-36), King Faisal Specialist Hospital & Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia; Tel: (01) 442-7248, or Fax: (01) 442-7237.

King Faisal Specialist Hospital & Research Centre Postgraduate Training Programs

King Faisal Specialist Hospital & Research Centre is pleased to invite applications for the following full-time postgraduate training programs:

1. Arab Board residency training in the specialties of internal medicine, obstetrics/gynecology, pediatrics, and surgery.
2. Five-year pathology residency training program affiliated with King Saud University, the Royal College of Pathologists of Australasia and the Royal College of Pathologists of Great Britain.
3. Fellowships are offered in the following areas: Cardiovascular Diseases; cardiology, pediatric cardiology, thoracic and cardiovascular surgery. Oncology; hematology, medical oncology, and pediatric hematology-oncology. Medicine; endocrinology, gastroenterology, infectious diseases, nephrology, pulmonology, critical care, and rheumatology. Pediatrics; allergy and clinical immunology, neonatal/perinatal medicine, gastroenterology and hepatology, infectious diseases, nephrology, neurology, genetics, metabolic diseases, and endocrinology.

For further information, contact: Director, Academic Affairs & Postgraduate Education (MBC-36), King Faisal Specialist Hospital & Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia; Tel: (01) 442-7214, or Fax: (01) 442-7237.

King Saud University Fellowship in Pathology

King Saud University announces the inception of a five-year joint fellowship training program in pathology. The training will be held at King Khalid University Hospital, King Faisal Specialist Hospital & Research Centre, Riyadh Armed Forces Hospital, King Fahad National Guard Hospital, and is a full-time fellowship training program. Application is open to interested and suitably qualified residents from all over the Kingdom of Saudi Arabia. To be eligible, applicants will meet the following criteria:

1. Doctors who hold an MB, BS from King Saud University or equivalent degree.
2. Doctors who have completed their internship in a recognized hospital.
3. Undergone successful completion of a selection examination and personal interview.
4. Applicants from other institutions should submit a letter from her/his employer that she/he will be sponsored during the entire period of training.

Application forms and inquiries should be forwarded to the Director of the Residency Training Program, College of Medicine, King Saud University, P.O. Box 2925, Riyadh 11461, Saudi Arabia, or contact the Residency Board secretary at Tel: 467-1551/1556/1564, or Fax: 481-1853.

First Annual Symposium of the Saudi Society of Allergy and Immunology, 1994

The First Annual Symposium of the Saudi Society of Allergy and Immunology will be held from 12 to 13 January 1994G(1 to 2 Sha'ban 1414H) in Riyadh, Saudi Arabia.

For further information, contact: Dr. Harb Harfi, King Faisal Specialist Hospital & Research Centre (MBC-58), P.O. Box 3354, Riyadh 11211, Saudi Arabia. Tel: (01) 464-7272 or Fax: (01) 442-7784.

Fifth Scientific Session, Saudi Heart Association, 1994

Abstracts of papers for presentation are being accepted for the Fifth Scientific Session of the Saudi Heart Association to be held from 25 to 27 January 1994G(14 to 16 Sha'ban 1414H) in Al-Khobar (Eastern Province) Saudi Arabia. Original work related to all aspects of cardiovascular diseases will be considered with particular emphasis on: 1. coronary artery disease; 2. valvular heart diseases; 3. pericardial disease; 4. interventional cardiology; 5. noninvasive cardiology; 6. infective endocarditis; 7. cardiac surgery; 8. pediatric cardiology; 9. cardiac anesthesia; and 10. congestive heart failure.

For further information regarding submission of abstracts, contact: Saudi Heart Association, College of Medicine, King Saud University, P.O. Box 2925, Riyadh 11461, Saudi Arabia. Tel: (966)(01)467-1556/1554, or Fax:(01)481-1853/467-1379.

Symposium on Organization of Perinatal Care in the Kingdom of Saudi Arabia, King Faisal University (KFU), 1994

The Symposium on Organization of Perinatal Care in the Kingdom of Saudi Arabia will be held from 1 to 2 February 1994G(21 to 22 Sha'ban 1414H) by King Faisal University (KFU), Dammam, College of Medicine & Medical Sciences (CMMS) Continuing Medical Education Program in Al-Khobar, Saudi Arabia.

The organizing committee invites colleagues to submit abstracts for presentation. Original topics related to any aspect of perinatal care organization will be considered with particular emphasis on: 1. planning of perinatal care; 2. role of hospital administration in perinatal care; 3. levels and functions of neonatal care services; 4. regionalization of perinatal care; 5. neonatal care facilities in KSA; 6. statistics and evaluation of perinatal care; 7. interrelation between obstetric care and neonatal care; 8. quality control in perinatal care; 9. neonatal and perinatal transport; 10. infection control in perinatal care; 11. perinatal nursing; 12. promotion of breastfeeding; 13. research issues in perinatal care; 14. follow-up of high risk neonates; and 15. personnel requirements.

The following guidelines for abstracts are: a) abstracts are not to exceed 250 words; b) should be typewritten on the abstract forms which will be provided upon request.

The following abstract format is as follows: 1. objectives; 2. methodology; 3. summarized results; and 4. conclusion (do not use abbreviations).

For further information, contact: Dr. Abdulatif Al Faraidy, Professor of Pediatrics & Chief of Neonatal Services, King Faisal University/Al-Khobar, P.O. Box 3775, Al-Khobar 31952, Saudi Arabia. Tel: (03) 898-4501/(03) 898-1189, or Fax: (03) 864-5972/(03) 857-4992.

Symposium on Surgical Emergencies, King Fahad Hofuf Hospital, 1994

A Symposium on Surgical Emergencies will be held from 1 to 2 February 1994G(21 to 22 Sha'ban 1414H) at King Fahad Hofuf Hospital, Hofuf, Al-Hassa, Saudi Arabia.

Distinguished speakers from world renowned institutions in addition to national and local speakers have been invited to cover the following topics: 1. management of critically ill patients in all surgical specialties; 2. general trauma; 3. specific trauma in all surgical specialties; and 4. non-traumatic surgical emergencies.

For further information, contact: Department of Continuing Education & Postgraduate Studies, King Fahad Hofuf Hospital, P.O. Box 3967, Hofuf, Al-Hassa, Saudi Arabia. Tel: (966) (03) 582-2400, (966) (03) 586-0000, extension 1740, and (966) (03) 586-3121, extension 2970, Fax: (966) (03) 582-2400, or Telex: 861107 KFHH-SJ.

Gastrointestinal Ultrasound Course, Department of Postgraduate & Academic Affairs, Riyadh Armed Forces Hospital, 1994

A Gastrointestinal Ultrasound Course will be held from 1 to 2 February 1994G(21 to 22 Sha'ban 1414H) by the Departments of Gastroenterology, Radiology, and Department of Postgraduate & Academic Affairs in collaboration with the Saudi Gastroenterology Association at Riyadh Armed Forces Hospital.

A series of courses including: Physics of Ultrasound, Ultrasound of the Liver and Biliary System, Abdominal Vessels, Pancreas, Spleen and Lymph Nodes, Pathology of the Gallbladder, Pancreas and Spleen, Interventional Ultrasound, General Ultrasound, Endoscopic Ultrasound, and Practical Training will be presented by distinguished national and international speakers.

For further information, contact: Department of Postgraduate & Academic Affairs, Riyadh Armed Forces Hospital, P.O. Box 7897, Riyadh 11159, Saudi Arabia. Tel: (966) (01) 477-7714, extensions 4933/4934/4935/4936/4937/ 4938, or Fax: (966) (01) 478-4057/478-1017.

International Symposium on Health Administration for Physician Executives, Security Forces Hospital, Riyadh 1994

The International Symposium on Health Administration for Physician Executives will be held from 5 to 8 February 1994G (25 to 28 Sha'ban 1414H) at Security Forces Hospital, Riyadh.

This symposium is intended to provide the opportunity for physician administrators to share experiences and gain insight in selected aspects of hospital administration and create a positive public image of physicians as health care administrators. A series of lectures including: Strategic Planning, Organizational Behavior, Quality Management, Performance Appraisal, Cost Benefit/Effectiveness, Medical Ethics, Technology Assessment, Managing Information, and Leadership in Medical Administration will be presented by local and international speakers.

For further information, contact: Education & Training, Security Forces Hospital, P.O. Box 3643, Riyadh 11481, Saudi Arabia. Tel: (966) (01) 477-4480, extension 2210, or Fax: (966) (01) 476-4757.

Eighth Asian Congress of Pediatrics New Delhi, India, 1994

The Eighth Asian Congress of Pediatrics will be held from 6 to 11 February 1994G(26 Sha'ban to 1 Ramadan 1414H) in New Delhi, India .

For further information, contact: Professor RK Puri, Secretary General, Eighth Asian Congress of Pediatrics, Department of Pediatrics, Maulana Azad Medical College, New Delhi-110 002, India. Tel: (0091)(11)331-6031/6660, or Fax: (0091)(11)228-3364.

Trauma & Critical Care Annual Postgraduate Course, Caesars Palace, Las Vegas, Nevada, USA 1994

Trauma & Critical Care-1994 will be held from 14 to 16 March 1994G(4 to 6 Ramadan 1414H) at Caesars Palace, Las Vegas, Nevada, USA. This annual postgraduate course in the management of trauma is sponsored by the American College of Surgeons Western States Committee on Trauma. Now in its 27th year, this course offers comprehensive continuing education in the treatment of seriously injured patients, stressing current methods of diagnosis and management. The faculty is composed of leading experts in the field of surgery for trauma. Accreditation: 21 Category 1.

For further information, contact: Dr. Kenneth L. Mattox, One Baylor Plaza, Houston, Texas 77030, USA. Tel: (713) 798-4557, or Fax: (713) 796-9605.

Symposium on Recent Advances in Obstetrics & Gynecology, Department of Obstetrics & Gynecology, Department of Academic Affairs & Postgraduate Education, King Faisal Specialist Hospital & Research Centre, 1994

A Symposium on Recent Advances in Obstetrics & Gynecology will be held from 5 to 6 April 1994G(24 to 25 Shawwal 1414H) at the new Postgraduate Centre, King Faisal Specialist Hospital & Research Centre.

Topics to be addressed are intended to cover: Management of Fetal Problems and Recent Developments in Gynecologic Cancer. A series of keynote lectures will be presented by invited international speakers.

Abstract topics for selection include: Fetal Abnormalities, Normal and Abnormal Labor, Abnormal Pregnancy, Intrauterine Fetal Therapy, Gestational Trophoblastic Tumors including Chemotherapy and New Radioimmunoassays, Screening for Gynecological Cancer including Tumor Markers and Radical versus Conservative Surgery. The deadline for submission of abstracts is 1 December 1993G(18 Jumada Al-Thani 1414H).

Overseas participants must obtain visa appplication forms provided by Academic Affairs & Postgraduate Education by 15 January 1994G(4 Sha'ban 1414H).

For further information, contact: Academic Affairs & Postgraduate Education (MBC-36), King Faisal Specialist Hospital & Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia. Tel: (966) (01) 442-7238, or Fax: (966) (01) 442-7237, or contact the Department of Obstetrics & Gynecology (MBC-52), Tel: (966) (01) 442-7392, or Fax: (966) (01) 442-7393.

International Symposium on Recent Advances in Otolaryngology Head and Neck Surgery, King Fahad National Guard Hospital, 1994

The International Symposium on Recent Advances in Otolaryngology Head and Neck Surgery sponsored by Saudi Arabian National Guard (SANG) will be held from 10 to 12 April 1994G(29 Shawwal to 1 Dhu Al-Qa'da 1414H) at King Fahad National Guard Hospital, Riyadh, Saudi Arabia.

Guest faculty includes: Prof. Ugo Fisch (Switzerland), Prof. WP Gibson (Australia), Dr. John W. House (USA), Dr. Ivo P. Janecka (USA), and Dr. John NG Evans (UK).

A call for scientific papers, new innovations, video tape demonstrations, and scientific posters are invited. No registration fee required.

For further information, contact: Dr. SA Kamal, Chairman, Scientific Committee, P.O. Box 22490, Riyadh 11426, Saudi Arabia. Tel: (966) (01) 252-0088, extension 2340, or Fax: (966) (01) 252-0088, extension 2329.

XXV Congress of the International Society of Hematology, Cancun, Mexico, 1994

The XXV Congress of the International Society of Hematology will be held from 17 to 22 April 1994G(6 to 11 Dhu Al-Qada 1414H) in Cancun, Mexico.

For further information, contact: XXV Congress of the International Society of Hematology, Blvd. Dias Ordaz 808, 72530 Puebla, Mexico. Tel:(052-22)438-100 y 373-607, or Telefax:(052-22).

Symposium on Emergency Medical Services in Saudi Arabia, Department of Polyclinics/Emergency Services, and the Department of Academic Affairs & Postgraduate Education, King Faisal Specialist Hospital & Research Centre, 1994

A Symposium on Emergency Medical Services in Saudi Arabia will be held from 19 to 20 April 1994G(8 to 9 Dhu Al-Qa'da 1414H) at the new Postgraduate Centre, King Faisal Specialist Hospital & Research Centre.

Topics to be addressed are intended to cover organization, clinical, training, and research in Emergency Medical Practice. A series of keynote lectures will be presented by invited international speakers.

Abstract topics for selection include: 1. Organization, standards, and communications in Pre-Hospital Care; 2. Organization, staff, utilization, and management in Emergency Systems; Emergency Medicine Training and Education; 3. Research in Emergency Medicine in Saudi Arabia; 4. Epidemiology of Emergency Medicine in Saudi Arabia (patterns of use, disease prevalence, and treatment standards); 5. Quality Assurance in Emergency Systems; and 6. other aspects pertaining to Emergency Care. Deadline for submission of abstracts is 30 January 1994G(19 Sha'ban 1414H).

Overseas participants must obtain visa application forms provided by Academic Affairs & Postgraduate Education by 15 January 1994G(4 Sha'ban 1414H).

For further information, contact: Academic Affairs & Postgraduate Education (MBC-36), King Faisal Specialist Hospital & Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia. Tel: (966) (01) 442-7238, or Fax: (966) (01) 442-7237, or contact the Department of Polyclinics/Emergency Services (MBC 62), Tel: (966) (01) 454-7272, extension 1860, or Fax: (966) (01) 442-7397.

First International Congress on Maxillofacial Prosthetics Palm Springs, California, USA, 1994

The First International Congress on Maxillofacial Prosthetics will be held from 27 to 30 April 1994G(16 to 19 Dhu Al-Qada 1414H) in Indian Wells, California, USA.

Major topics include: (a) Restoration of mandibular, maxillary and facial defects; (b) Dental management of the irradiated patient: (c) Use of osseointegrated implants and free flaps in restoration of oral-facial defects; (d) Treatment of osteoradionecrosis - current concepts; (e) Materials in maxillofacial prosthetics; and (f) Osseointegrated implants in irradiated patients.

The Congress is sponsored by: 1. UCLA Maxillofacial Prosthetic Hospital Dentistry Group - Los Angeles, CA, USA; 2. Memorial Sloan-Kettering Cancer Center Dental Service - New York, NY, USA; and 3. Cleveland Clinic Foundation, Department of Dentistry - Cleveland, Ohio, USA.

A call for abstracts has been issued and interested participants should contact R.E.S. Seminars for applications. The deadline is 30 November 1993.

Many individuals internationally may be prevented from attending because of high cost of travel. Therefore, an international travel subsidy program has been established to assist interested individuals. Travel awards of up to US$750.00 are available. Priority will be given to those persons who hold full time appointments in Universities or Government Sponsored Clinics and residents in training. Those interested should contact the Congress Secretary, before October 1, 1993. Include a C.V., a letter of support from your Chairperson and/or Dean or other appropriate individuals. Those receiving awards will still be responsible for registration fees and all other expenses.

For further information, contact: R.E.S. Seminars, P.O. Box 99199, San Diego, CA, USA 92109, or Fax: 001-619-272-7687.

VII International Congress of Pediatric Dermatology, Buenos Aires, Argentina, 1994

The VII International Congress of Pediatric Dermatology will be held from 26 September to 1 October 1994G(21 to 26 Rabi Al-Thani 1415H) in Buenos Aires, Argentina.

Topics to be addressed are intended to cover atopic dermatitis, nutritional disorders, AIDS, and genodermatoses.

For further information, contact: Dr. Adrian M. Pierini, President, VII International Congress of Pediatric Dermatology, Arenales 1446 Ap. 1B, (1061) Buenos Aires, Argentina. Tel: (54.1) 814-4068, or Fax: (54.1) 812-9255.

Fourth International Course on Magnetic Resonance Imaging, Riyadh Armed Forces Hospital, 1994

The Fourth International Course on Magnetic Resonance Imaging (MRI) will be held from 2 to 5 October 1994G(27 to 30 Rabi Al-Thani 1414H) by the Departments of Radiology, Medical Physics and Medical Studies of the Riyadh Armed Forces Hospital.

The course will provide an overview of MR Technology and basic principles, current and future applications of MR in the whole body. Current and potential applications of MR in the spectroscopy will also be discussed. Small group workshops on Basic Physics, Neurological Applications, Musculoskeletal, and Genitourinary Systems will be provided for all participants.

For further information, contact: Department of Medical Studies, Riyadh Armed Forces Hospital, P.O. Box 7897, Riyadh 11159, Saudi Arabia. Tel: (966) (01) 477-7714, extensions 2289/2269, or Fax: (966) (01) 477-7194/477-9168.

Special Acknowledgment

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Corrections

In the *Original Article* by Al-Ballaa et al, "Pattern of Adult Onset of Polymyositis and Dermatomyositis and Association With Malignancy" (1993;13(6):525-29), the first author should read as: Suliman R. Al-Balla, FRCP(C). The Author Index on page 583 should read as: Al-Balla SR, 246,259,525 and, Al-Ballaa, SR, 246,259.

In the *Letters to the Editor* by Saeed et al, "Molecular and Regional Observations Related to Hepatitis C Virus in Egyptian Blood Donors" (1993;13(6):568-69), the second paragraph, sentences 1 and 2 should read as follows: A nested polymerase chain reaction (PCR) amplification [2] for the detection of HCV-RNA was used on 33 of the 76 EIA-2 positive donations. HCV-RNA could be detected in 19 (83%) of 23 RIBA-2 positive donations and thus confirmed the presence of HCV infection.

Please note these corrections in your copies of the November 1993 issue of the *Annals*.

عمليات اغتراس الكلى في مستشفى الملك فيصل التخصصي ومركز الأبحاث الرياض، ١٩٨٧ ـ ١٩٩١م، تحليل البقيا وتواتر الرفض والمضاعفات الجراحية

أجريت خلال فترة السنوات الخمس من ١٩٨٧م إلى ١٩٩١م مائة وواحدة وستون عملية اغتراس كلية في مستشفى الملك فيصل التخصصي ومركز الأبحاث: ٧٩ كلية من متوفين و٨٢ كلية من متبرعين أحياء ذوي قربى. تم الحصول على جميع الكلى المأخوذة من متوفين، باستثناء واحدة، من داخل المملكة العربية السعودية، ومن مواطنين سعوديين في ٦٧٪ كان نظام العلاج المثبط للمناعة مركبًا من عقاقير ثلاثة هي السايكلوسبورين ـ أ والآزاثيوبرين والبريدنيسون. تظهر الجداول الإحصائية أن نسب بقيا الطعم بعد سنة واحدة وثلاث سنوات ٨٥٪ و٧٦٪ بالنسبة للكلى المأخوذة من المتوفين و٩٦٪ و٩١٪ على التوالي بالنسبة للكلى المأخوذة من الأحياء ذوي القربى ($P < ٠,٠١$). أما نسب البقيا المقابلة فكانت ٩٧٪ و٩٤٪ للكلى المأخوذة من المتوفين و٩٩٪ و٩٧٪ للكلى المأخوذة من الأحياء ذوي القربى. وهي نتائج جيدة تضاهي أفضل النتائج في العالم الغربي. كانت المضاعفات الجراحية الأشد خطورة هي الخثار الوعائي (خمس حالات) وتلوث خط المفاغرة الشرياني مع نزف (حالتان)، مما أدى إلى خسارة كلية مأخوذة من متوفٍ في جميع هذه الحالات. كان السبب الأكثر شيوعًا للوفاة هو الخمج بالحُمات: الحماق ـ حمة الخلايا الضخمة والتهاب الكبد ب وج. مازالت نسبة التبرع بالأعضاء بعد الوفاة ومن الأقارب الأحياء منخفضة في المملكة العربية السعودية، ونقص الأعضاء هو العائق الرئيسي أمام التوسع في هذا النشاط الناجح. إن التعليم المستمر للهيئات الطبية المكونة من جنسيات عديدة بالإضافة إلى عامة الناس ضروري لتحسين الوضع.
المدونات الطبية السعودية ١٩٩٤م، ١٤ (١): ٥ ـ ١١.

الاختلاف الموسمي لداء البروسيلات إيجابي المزرعة في مستشفى جامعي كبير في الرياض، المملكة العربية السعودية

داء البروسيلات هو أحد الأمراض الرئيسية حيوانية المصدر في العالم. وقد اعتبر هذا الداء مشكلة صحية رئيسية في المملكة العربية السعودية في عام ١٩٨٣م، وتم منذ ذلك الحين اتخاذ العديد من الإجراءات للسيطرة عليه. أجرينا دراسة لتحديد معدل الوقوع السنوي والاختلاف الموسمي لداء البروسيلات المثبت بزرع الدم (حالات البروسيلا) الذي تم تشخيصه في مستشفى الملك خالد الجامعي بالرياض خلال الفترة من عام ١٩٨٥م إلى عام ١٩٩١م. وقد أظهرت النتائج انخفاض معدل وقوع حالات البروسيلا إلى الخمس في خلال سنوات الدراسة السبع: من ٨,٦ حالة/ ١٠٠٠ حالة تنويم في عام ١٩٨٥م إلى ١,٤ حالة/ ١٠٠٠ حالة تنويم في عام ١٩٩١م. كان انتشار المرض مستمرًا طوال العام ولكن معظم الإصابات حدثت في الربيع والصيف وأوائل الخريف. وتجري مناقشة الأسباب المحتملة للاختلاف الموسمي وانخفاض وقوع حالات البروسيلا التي لوحظت في هذه الدراسة.
المدونات الطبية السعودية ١٩٩٤م، ١٤ (١): ١٢ ـ ١٥.

تقلقل الورك لدى الولدان في المملكة العربية السعودية النتائج وجدوى التكلفة لبرنامج تقصٍ مدته احد عشر عامًا

بالرغم من أن مزايا تقصي حالة الورك إبان الولادة بحثًا عن الخلع الولادي قد تأكدت مرارًا، إلا أنه أثيرت بعض الشكوك حول الحاجة إلى تجبير جميع الحالات الإيجابية. وتعرض هذه الدراسة الخبرة المستقاة من برنامج التقصي الحالي المتواصل منذ ما ينوف عن ١١

سنة وخاصة فيما يتعلق بالفائدة مقابل تكاليف التقصي والتدخل الجراحي المبكر. من بين ٣٠٦٥١ مولود حتى تم فحصهم لتحري الخلع الولادي للورك باستخدام حركات بارلو وأورتولوني، اكتشفت ١٣٢ حالة إيجابية، وبذلك يتراوح الوقوع بين ٢ و٦ من كل ١٠٠٠ ولادة حية، أي ما متوسطه ٤,٢ من كل ١٠٠٠ خلال الفترة. تناقش هذه الدراسة مغزى الملاحظات الوبائية والسريرية بالنسبة للعلاج. كما تم حساب تكلفة التقصي والعلاج الجراحي للحالات التي لا يتوقع شفاؤها بدون تجبير، حتى مع الافتراض بأن ثلاث من أربع حالات يمكن أن تشفي بدون تدخل. كانت فعالية التكلفة لبرنامج تقصي الخلع الولادي للورك واضحة من هذه الدراسة التي استمرت ١١ سنة، مما يبرر تمامًا الاستمرار في هذا البرنامج فضلاً عن المعاناة الإنسانية التي قد تنجم عن غياب التشخيص.
المدونات الطبية السعودية ١٩٩٤م، ١٤ (١) ١٦ ـ ١٨.

نشوء خراجات تحت الجلد ناجمة عن المتفطرة البقرية بعد التلقيح ضد الدرن والتهاب الكبد «ب»

يشكل التلقيح ضد التهاب الكبد «ب» والدرن جزءًا من برنامج التمنيع الوطني في المملكة العربية السعودية. وقد تم إدخال التلقيح ضد التهاب الكبد «ب» في منطقة مكة المكرمة في شهر يناير ١٩٩١م، ومنذ ذلك التاريخ أصيب ٢٥ طفلاً بعد التلقيح بخراجات تحت الجلد في موقع التلقيح. أثبتت الدراسات الجرثومية أن هذه الخراجات ناشئة عن عصية «كالميت غيران». نجعت المعالجة لدى عشرة مرضى بعقاري آيسونيازيد وريفامبيسين ولدى ١٥ مريضًا بعقار آيسونيازيد فقط. احتاج أربعة مرضى إلى شق الخراج ونزحه. تناقش هذه الدراسة الأسباب المحتملة لهذه المضاعفة لدى مرضانا.
المدونات الطبية السعودية ١٩٩٤م، ١٤ (١): ١٠ ـ ٢١.

دراسة استطلاعية عن طراز المراضة لمن عوينوا في مركز الرعاية الأولية بمستشفى الملك خالد الجامعي، الرياض، المملكة العربية السعودية

هناك ندرة أو غياب للمعلومات عن طراز المراضة لمن عوينوا في مراكز الرعاية الأولية في معظم بلدان الشرق الأوسط بما في ذلك المملكة العربية السعودية. لذا أجريت دراسة استطلاعية على جميع المرضى الجدد في مركز الرعاية الأولية بمستشفى الملك خالد الجامعي، الرياض، المملكة العربية السعودية، خلال عام واحد (١٩٩١ ـ ١٩٩٢م). ونورد هنا تحليلاً عن طراز المراضة لدى ٩٤٤١ مريضًا جديدًا تمت معاينتهم خلال تلك الفترة. كان غالب المرضى عمومًا من الذكور وكان أكثر من ٧٠٪ من المرضى دون سن الأربعين. شكلت الأمراض غير المحددة والأمراض الجلدية والبولية التناسلية والهضمية والعضلية الهيكلية والتنفسية أكثر من ٧٠٪ من الحالات لدى المرضى. أحيل ثلث المرضى تقريبًا، خصوصًا أولئك الذين يعانون من أمراض جلدية وبولية تناسلية، لتلقي رعاية تخصصية. ومن المعقول أن يطرأ تغير على الطراز الشائع للأمراض والملاحظ في هذه الدراسة مع الوقت نتيجة للتدخلات التي تتبناها مراكز الرعاية الأولية أو نتيجة للتطور الاجتماعي أو كنتيجة تراكمية لكلا العاملين معًا. ويتعين على طبيب الرعاية الأولية أن يكون مدركًا لمثل هذا التغير وذلك بإجراء تحليل دوري للمعلومات المتوافرة عن طراز المراضة.
المدونات الطبية السعودية ١٩٩٤م، ١٤ (١): ٢٢ ـ ٢٥.

مآل لدغة الأفعى في منطقة الباحة
مع التركيز على مضاعفات الإرقاء

شوهد في مستشفى الملك فهد بالباحة إثنان وثمانون مريضًا ممن لدغتهم الأفاعي خلال الفترة بين عام ١٩٨٣م و١٩٨٩م، وتمت مراجعة ملفاتهم على نحو استعادي. كانت أكثر الأعراض الألم (٨٠,٥٪) والتورم (٧٧٪). وجدت شذوذات الإرقاء لدى ٣٦ مريضًا (٤٤٪) وكانت موجودة لدى دخول المستشفى عادة ولكن تأخر ظهورها أحيانًا إلى ما بعد الدخول بأربع وعشرين ساعة. عانى جميع المرضى من تورم موضعي، كما عانى سبعة عشر منهم من انخفاض الهيموغلوبين وتسعة وعشرون من كثرة الكريات البيض، الأمر الذي يشير إلى انتشار السمم. ظهر نخر موضعي في الجلد على خمسة مرضى، تطلبت حالات ثلاث منهم بضع اللفافة بسبب متلازمة تضيق الحيز العضلي. استجاب جميع المرضى للمعالجة (مضادات السمم أو منتجات المصورة أو كلاهما) باستثناء حالة وفاة واحدة. تؤكد هذه البيانات على أن الشذوذ الإرقائي هو المضاعفة الرئيسة لعضة الحية في منطقة الباحة في المملكة العربية السعودية.

المدونات الطبية السعودية ١٩٩٤م، ١٤ (١): ٢٦ ـ ٢٩.

خراجات دماغية متعددة في مستشفى الملك خالد الجامعي ـ تقارير عن ست حالات

راجع المؤلفون ست حالات من الخراجات المتعددة في الدماغ والتي عولجت في مستشفى الملك خالد الجامعي على مدى ثماني سنوات. كانت نسبة هذه الخراجات ٢٢٪ من إجمالي خراجات الدماغ التي عولجت خلال الفترة ذاتها. كانت هذه المجموعات غير عادية إذ كانت العوامل الممرضة تتكون من الفطريات البدروسية (Fonsecaea Pedrosoi) في مريضين (٣٣٪) ومن الفطريات الشعاعية مثل (Nocardia Asteroides) في مريض واحد (١٦٪). عولج مريضان تخبريا بالمضادات الحيوية في مكان آخر لمدة شهر واحد وتوفي الأول بعد ثلاثة أيام والثاني بعد ٢٨ يومًا من دخول المستشفى. قد يكون المآل السيىء ذا علاقة بتأخر الوصول إلى التشخيص الجرثومي وبدء تطبيق العقاقير المضادة الملائمة. تشير هذه الدراسة إلى أهمية التعرف المبكر على الجراثيم الممرضة في المرضى الذين يعانون من خراجات دماغية متعددة.

المدونات الطبية السعودية ١٩٩٤م، ١٤ (١): ٣٠ ـ ٣٢.

استئصال المرارة بتنظير جوف البطن ـ تجربة السنة الأولى

أُدخل ما مجموعه ٣٠٧ من المرضى تباعًا إلى المستشفى لاستئصال المرارة بسبب حصيات مصحوبة بأعراض. وقد اعتبر مائتان وسبعون من هؤلاء المرضى (٨٨٪) ملائمين لاستئصال المرارة بتنظير جوف البطن. أُدخل ٤٢ مريضًا (١٧٪) منهم في حالة إسعاف. تم بنجاح إجراء الاستئصال بالتنظير لدى ٢٤٦ مريضًا (٩١٪) في حين اضطررنا إلى التخلي عن التنظير واستبداله بعملية فتح البطن لاستئصال المرارة لدى من تبقى من المرضى (٢٤ مريضًا، ٩٪) حدثت مضاعفات بعد العملية، معظمها طفيف، لدى ٢٢ مريضًا (٩٪). وفيما يتعلق بحصيات القناة الصفراوية الجامعة المشتبه فيها أجري تنظير داخلي مع تصوير راجع للمعثكلة والقنوات الصفراوية قبل الجراحة. كان متوسط مدة العملية ٨٢ دقيقة، وغادر ٧٠٪ من المرضى المستشفى في غضون ٤٨ ساعة بعد العملية وأكثر من ٩٠٪ من المرضى في غضون ثلاثة أيام. تشير هذه النتائج إلى أن استئصال المرارة بتنظير جوف البطن أمر ممكن لدى غالبية المرضى الذين يعانون من حصيات مصحوبة بأعراض في المرارة.

المدونات الطبية السعودية، ١٩٩٤م، ١٤ (١): ٣٣ ـ ٣٦.

دور التدعيم في قالب وظيفي في علاج كسر كولز

نقدم في هذا المقال نتائج مائة حالة متعاقبة من كسور كولز عولجت بالتدعيم في قالب وظيفي وفي وضع الاستلقاء كما جاء في إرشادات سارمينتو، وذلك باستخدام متمفصلات معدنية صنعت محليًا، وتابعنا هذه الحالات لمدة ١٨ أسبوعًا. قمنا بمقارنة هذه النتائج مع النتائج التي توصل لها المؤلفون الآخرون الذين استخدموا التدعيم في قالب وظيفي وكذلك الذين استخدموا الطرق المحافظة التقليدية بما في ذلك طريقة التدبيس عبر الجلد. تبين وجود اختلافات واسعة بين النتائج التي توصل إليها مختلف المؤلفين الذين استخدموا أساليب متنوعة، إلا أن طريقتنا في استخدام التدعيم في قالب وظيفي في وضع الاستلقاء كانت على العموم ضمن أفضل الدراسات التي قدمت.

المدونات الطبية السعودية ١٩٩٤م، ١٤ (١): ٣٧ ـ ٤١.

معالجات التهاب المثانة النزفي العصي والناجم عن السايكلوفسفاميد بإرواء المثانة المتواصل بالبروستغلندين و ـ ٢ ـ ألفا

نقدم في هذه المقالة الاستعمال الناجح للبروستغلندين و ـ ٢ ـ ألفا في الإرواء المتواصل للمثانة لدى مريضين عانيا من التهاب المثانة النزفي الناجم عن السايكلوفسفاميد والعصي على المعالجة التقليدية المحافظة. استخدم محلول البروستغلندين و ـ ٢ ـ ألفا بنسبة ٠,٧ مغ٪ في الإرواء المتواصل للمثانة بمعدل ١٥٠ إلى ٢٠٠سم معكب/ ساعة لمدة أربعة أيام. كانت الاستجابة تامة عند المريضين ولم تلاحظ أية تأثيرات جانبية.

المدونات الطبية السعودية ١٩٩٤م، ١٤ (١): ٤٢ ـ ٤٤.

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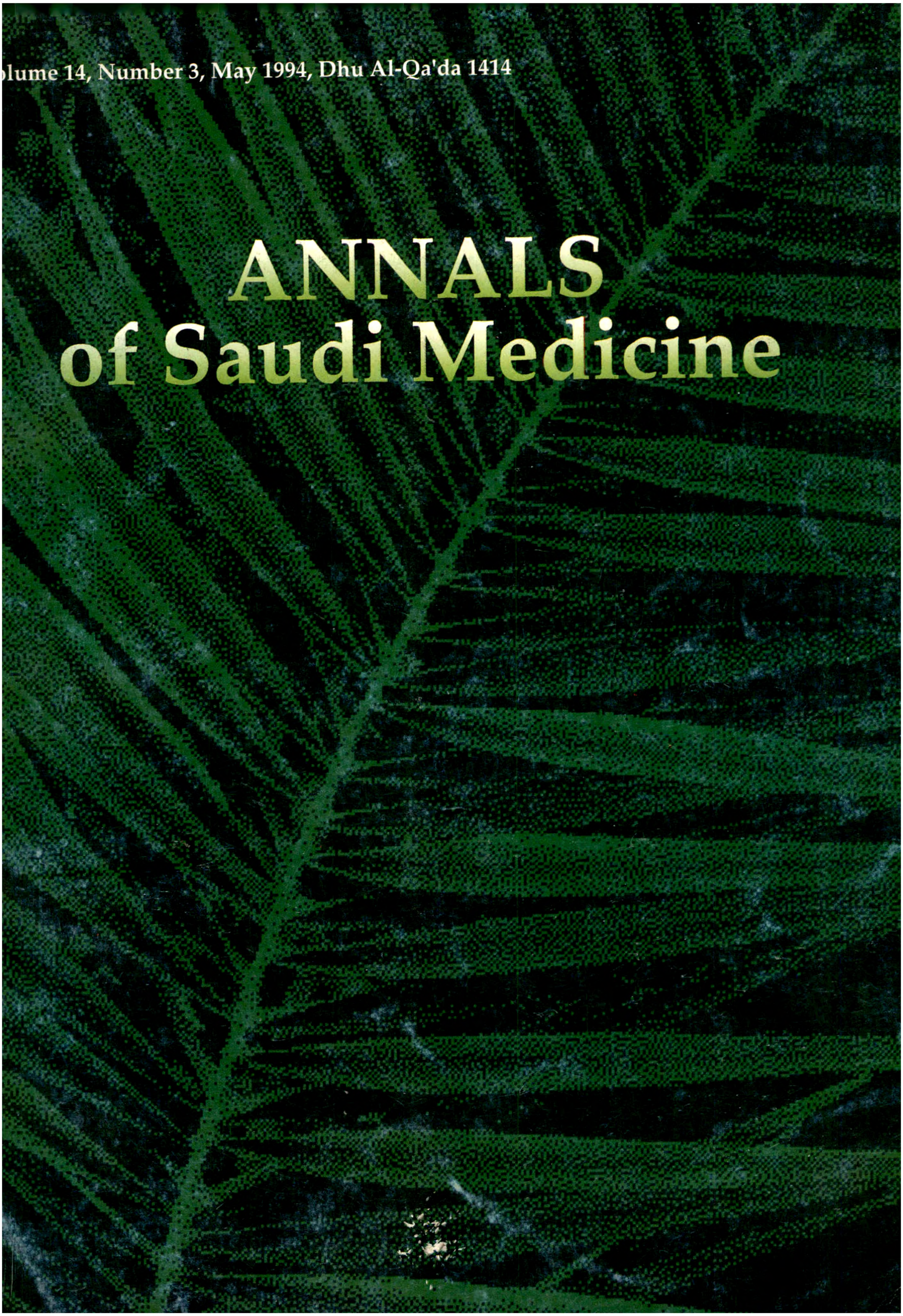

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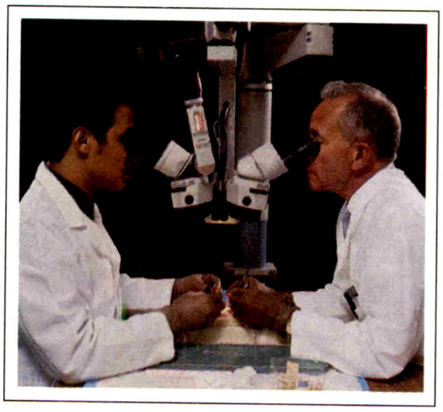

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King Faisal Specialist Hospital and Research Centre
P.O. Box 3354, Riyadh 11211, Saudi Arabia
Telephone: 442-72-14 or Fax: 442-72-37

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Editorial

IT SHOULD BE POSSIBLE TO ELIMINATE PEPTIC ULCER DISEASE AND GASTRIC CARCINOMA FROM SAUDI ARABIA

Until recently, it would have been unthinkable to suggest that it might be possible to eliminate peptic ulcers and gastric carcinoma from the Kingdom of Saudi Arabia. This possibility now deserves serious consideration. This change in thinking is a direct result of recent studies linking the seemingly different diseases to an infection with a bacterium, *Helicobacter pylori*. *H. pylori* infection has been linked to gastric carcinoma, peptic ulcer disease, and gastric B-cell lymphoma.[1-5] The tremendous morbidity and mortality from *H. pylori* infection are only now becoming appreciated. The cumulative risk of developing a peptic ulcer is 15% to 20% and 0.5% to 1% risk of developing gastric carcinoma. The risk of gastric lymphoma is unknown. Overall, the recognized rate of mortality or morbidity related to *H. pylori* infection is 20% to 30% of those infected.

It has long been appreciated that chronic atrophic gastritis was a precursor lesion to gastric carcinoma and that, in areas of the world where atrophic gastritis was common in young adults, gastric cancer was frequent. Gastritis was also known to be almost universally present in patients with gastric or duodenal ulcer disease.[2,6,7] Studies of the epidemiology of these gastritis-associated diseases demonstrated that unidentified environmental factor(s) were involved in development of gastritis and in progression from atrophic gastritis to gastric cancer. Despite a large number of studies and clues such as differences in prevalence of gastritis depending on socioeconomic class, ethnic group, age, implicating environmental factors, no common theme or factor emerged until approximately 10 years ago when *H. pylori* was cultured from the gastric mucosa of patients with gastritis and ulcer disease. It was subsequently shown that ingestion of *H. pylori* resulted in gastritis and that gastritis improved and even actually reversed following eradication of the infection.[8-10]

Over the last decade, *H. pylori* has become established as the major cause of gastritis in humans. Recently, a number of investigators have conclusively demonstrated that eradication of the *H. pylori* infection effectively cures peptic ulcer disease.[11-20] In this instance, "cure" means that the natural history of ulcer disease changes, as ulcers do not recur. Thus, no *H. pylori*, no ulcer.[7]

H. pylori, gastritis, and gastric carcinoma: The latent period between development of atrophic gastritis and gastric carcinoma is measured in decades, whereas the latent period for peptic ulcer is shorter.[21] It follows that the spectrum of *H. pylori*-related disease present in a population reflects the average age of acquisition of the infection.[1,22] In developing countries, the majority of individuals acquire *H. pylori* infection in early childhood and, as a result, atrophic gastritis is common in mid-life. In developed countries, gastric carcinoma is typically a disease of the elderly and reflects the fact that this group represents those who developed *H. pylori* infection in childhood as well as those who acquired it in adulthood.[21] In developing countries, gastric carcinoma is typically present in younger individuals. In one study from Saudi Arabia, gastric carcinoma was found to occur as early as age 20 and gastric carcinoma represented 27% of gastrointestinal cancers in Southern Saudi Arabia. The mean age of those with gastric cancer was only 42 years (Hamdi and Morad, personal communication). In another study, gastric carcinoma represented 31% of gastrointestinal malignancies.[23] A pattern of gradually increasing age of the diagnosis of gastric carcinoma is typically the result of a change in the age of acquisition of *H. pylori* infection in a population.

Although the epidemiology evidence linking gastric carcinoma and *H. pylori* is now quite strong,[1,24-39] can we use that information to reduce the risk of gastric carcinoma? The risk of developing gastric cancer increases with the severity of gastritis and is highest with the most advanced stages. Complete gastric atrophy cannot be reversed by eradication of *H. pylori* infection but progression to this late stage can be prevented. Although eradication of *H. pylori* infection leads to marked improvement in histologic gastritis, it is not yet known if there is a point beyond which the changes become irreversible. It is also not proven that eradication of the infection and improvement of gastritis will result in a reduction in the risk of gastric cancer. Although it is possible that whatever genetic damage to gastric mucosal cells that eventuates in gastric cancer takes place at an early time point in the infection, such a scenario seems unlikely.

There are now sufficient epidemiologic data to allow investigators to predict the prevalence of gastritis in different environments. In developing countries, the rate of acquisition of *H. pylori* infection is rapid, with most individuals becoming infected before age 20.[2,6,40-42] In contrast, in developed countries, the rate of infection is lower, and the available data suggests it has steadily decreased to where, in the higher socioeconomic groups, *H. pylori* is present in less than 20%, irrespective of age.[43] The epidemiology of *H. pylori*- associated diseases has also changed to where *H. pylori* infection and *H. pylori*-associated diseases are common only in the lower socioeconomic classes. Improvements in standards of living and in sanitation have resulted in a change in epidemiology of *H. pylori* infection. Around the world we are seeing the pattern change from that of a developing country to that of a Western developed nation.[21] Such a change can probably best be seen in Japan.[44] Japan has been recently transformed from a largely rural developing country to a modern industrial power. Studies of the epidemiology of *H. pylori* infection in Japan have shown that those born after 1950 have the prevalence pattern of a developed country with a relatively low rate of acquisition.[44] In contrast, those born prior to 1950 are almost all infected as would be expected, since they were born and acquired the infection in what was a developing country.

It is currently believed that childhood is the period of the greatest risk for acquisition of *H. pylori* infection. The prevalence of *H. pylori* infection in groups of adults is related to the socioeconomic status of their family during childhood; the prevalence of *H. pylori* infection is greatest in those from the lowest socioeconomic groups and least in those from the highest. Attainment of high socioeconomic status does not immediately confer an improvement in the epidemiology of *H. pylori* in either an individual or in a population. *H. pylori* is transmitted within families with children and, as noted above, the risk of acquisition is closely related to socioeconomic status in childhood.

The available data suggest that it requires several generations for the pattern of acquisition of infection to naturally change from that of a developing country (almost universal infection) to that of a westernized country (infrequent infection). The prevalence pattern of *Helicobacter pylori* infection in the Kingdom of Saudi Arabia is that of a developing country.[44-49] Thus, the Kingdom of Saudi Arabia can have a highly developed economy, excellent sanitation, and high standards of living and yet the citizens can retain the stomachs of inhabitants of an undeveloped nation.

Over time, the pattern of prevalence of infection in the Kingdom of Saudi Arabia will change and each successive generation will experience a progressively lower rate of acquisition. It may not be necessary to wait for the natural and gradual loss of *H. pylori* infection from a society. Instead, it should be possible to turn the clock ahead and experience the future because *H. pylori* gastritis is caused by a bacterial infection and that infection can be eradicated.

Eradication of *H. pylori* infection from the population should also result in elimination of gastritis and the gastritis-associated diseases, gastric ulcer, duodenal ulcer, and the intestinal type of gastric carcinoma. The tools needed to eradicate *H. pylori* infection are available. For example, there are two simple, noninvasive, efficient and complementary noninvasive methods to detect *H. pylori* infection that are serologic tests for the presence of anti-*H. pylori* IgG and the urea breath test. The urea breath test is based on the recovery of $^{13}CO_2$ in the breath after administration of urea labeled with the stable isotope of carbon ^{13}C.[50-53] The breath test is particularly valuable because it will also identify that eradication of the infection has occurred. Neither test is routinely available in the Kingdom of Saudi Arabia at the present time but both can be easily established.

It may be both feasible and cost effective to eradicate *Helicobacter pylori* from the population of the Kingdom of Saudi Arabia. The first step would be to perform a feasibility study in a test area. For example, a region with a defined population could be chosen and an epidemiology study of the prevalence of *H. pylori* infection performed. Eradication of the infection would then be attempted using available inexpensive antimicrobial therapy. The population would then be followed for several years to determine the rate of recurrence of the infection. The lessons learned in the trial would be used to plan additional trials leading to eventual eradication of the infection from the entire population. At the present time, it is not clear whether guest workers from developing countries would ultimately need to be treated to prevent the reintroduction of *H. pylori*. The experience from the United States with the continued influx of individuals from developing countries suggests that this may not be necessary but the question has not been studied prospectively.

Although all the tools needed to begin an eradication program are available, it is important to ask whether to do so would be cost effective. Ulcer disease and gastric cancer are common in the Kingdom of Saudi Arabia and account for major health care expenditures, in time lost from work, and in loss of valuable members of the population who die from the complications of ulcer or from gastric cancer. In the United States, therapy is primarily reserved for those with peptic ulcer disease because it is recognized that eradication of *H. pylori* infection results in accelerated ulcer healing, elimination of ulcer recurrence, elimination of the need for maintenance therapy, of ulcer surgery, and of ulcer complications. The smaller population of the Kingdom of Saudi Arabia, and the almost universal presence of the infection, suggests that eradication of the infection would be beneficial and should largely eliminate peptic ulcer disease with all its costs and complications as well as rapidly change the risk of developing gastric cancer. A program to eradicate *H. pylori* infection in Saudi Arabia deserves serious consideration.

David Y. Graham, MD
Baylor College of Medicine
Houston, Texas, USA
Souheil M. Shabib, MD
Department of Pediatrics (MBC-58)
King Faisal Specialist Hospital and
Research Centre.
P.O. Box 3354
Riyadh 11211, Saudi Arabia
Ibrahim Al-Mofleh, MD
King Saud University
P.O. Box 2925
Riyadh 11461, Saudi Arabia

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NONCARDIAC DEFECTS IN CHILDREN WITH CONGENITAL HEART DISEASE

Olufemi Jaiyesimi, FRCP(Lond), DCH(Lond); Dawala K. Ruberu, MRCP(UK), DCH(Lond)

During a 39-month period, we prospectively studied the noncardiac defects (NCD) in 320 Saudi children who presented to us with congenital heart disease (CHD). Ninety NCD were detected in 80 (25%) of the 320 patients. Recognized syndromes comprised 49 (54%) of the 90 NCD; Down syndrome alone accounted for 32 (65%) of the 49 syndromal defects. Next to syndromal defects were musculoskeletal (24.5%), neurological (9%) and gastrointestinal defects (8%). As expected, there was an association between Down syndrome and cardiac septal defects: 28 (87.5%) of the 32 patients with this syndrome had some form of septal defect, and 16 of the 17 cases of atrioventricular (AV) canal defect occurred in patients with trisomy-21. Overall, the NCD were considered to be moderately severe or severe in 67 (84%) of the 80 affected patients. Indeed, 48 (60%) of the 80 patients (or 15% of the original group of 320 patients) had varying degrees of mental retardation. The results of this study confirm the well-recognized association between trisomy-21 and cardiac malformation, and emphasize the need to search for such defects in any child with Down phenotype, and suggest that there is a relatively high incidence of serious NCD in children with congenital heart disease. Nationwide studies on birth defects are needed, and if they yield data similar to those from our present study, appropriate prevention strategies will have to be considered. *Ann Saudi Med 1994;14(3):183-186.*

Within the last two decades, rapid advances in health care provision have been made in the Kingdom of Saudi Arabia.[1] An example of this remarkable progress is the provision of excellent surgical care facilities for children with congenital heart disease (CHD), such that cardiac surgery is now a routine event in designated centers in the Kingdom. A complete medical examination, which is a prerequisite for cardiac surgery, entails the detection and evaluation of any associated noncardiac defects (NCD). In this regard, a knowledge of the general incidence and types of such NCD in a particular region would be useful since it could serve as a guide during the preoperative assessment of individual patients. We have therefore studied the NCD in Saudi children who presented to us with CHD and report our findings here.

Patients and Methods

During a 39-month period (August 1988 to October 1991), 320 Saudi children with CHD were prospectively studied in the Pediatric Cardiology Unit at King Fahd Specialist Hospital, Buraidah, Qassim Province. Details of the patients and methods have been described in the literature.[2] This present study involved those of the original 320 patients who had NCD.

In order to facilitate the analysis of our data, certain measures were adopted: 1. Syndromes encountered in the patients were classified as single defects, though many of them had multisystem manifestations; 2. Neurological defects were listed separately only if they did not fit into any recognized syndrome; and 3. The severity of the NCD was graded as follows: (minor) causes little or no handicap, poses no threat to life; (moderate) causes moderate handicap and/or threat to life; (major) major handicap defect, potentially fatal. The mental development of each patient was assessed by simple routine clinical methods; elaborate developmental tests were not performed.

Results

Incidence

Of the 320 children with CHD, 80 (25%) had associated NCD. These 80 comprised 41 males and 39 females, and their mean age at diagnosis (17.4 ± 24.7 mo.) did not differ significantly from that (24.6 ±36.9 mo.) of the 240 patients who had no associated defects. In all, 90 NCD were detected in the 80 patients.

Table 1 shows the incidence and type of NCD in patients with various forms of CHD. All 17 patients with atrioventricular (AV) canal defect had NCD; namely, Down syndrome (16 patients) and Marfan syndrome. One-third of the patients with aortic stenosis (AS) had NCD, as did a similar proportion of those with Fallot tetralogy. By contrast, the incidence of NCD in patients with pulmonary valve stenosis was comparatively low (10%), and only one

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From the Departments of Pediatric Cardiology (Dr. Jaiyesimi) and Pediatrics (Dr. Ruberu), King Fahd Specialist Hospital, Buraidah.

Address reprint requests and correspondence to Dr. Jaiyesimi: King Fahd Specialist Hospital, P.O. Box 2290, Buraidah, Saudi Arabia.

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of the 25 patients with persistent ductus arteriosus had NCD.

Types of Defects

Recognized syndromes accounted for 49 (54%) of the 90 NCD (Table 2). The spectrum included both the common (e.g., Down syndrome) and the uncommon, such as Williams syndrome.[3] There was one case each of the following syndromes: asplenia,[4] Kartagener,[5] Holt-Oram, Marfan, and scimitar.[6] There were varying degrees of mental retardation in 42 of the 49 patients in this group.

There were 22 musculoskeletal defects, among which were facial dysmorphism (8 cases), defects of the palate and/or lip (3 cases), choanal atresia (3 cases), and inguinal hernia (3 cases). In addition, there was one case each of exomphalos minor, eventration of the diaphragm, osteopetrosis, syndactyly, and hypertrophy of the right upper and lower limbs (hemihypertrophy).

Eight patients had nonsyndromal neurological defects; namely, microcephaly (3 cases), hydrocephalus (1 case), and two cases each of congenital squint and unclassified mental deficiency.

TABLE 1. *Incidence of noncardiac defects (NCD) in patients with various types of congenital heart disease (CHD).*

Type of CHD	No. of patients	Patients with NCD (%)	
Ventricular septal defect (VSD)	123	29	(24)
Atrial septal defect (ASD)	37	9	(24)
Pulmonary valve stenosis (PS)	29	3	(10)
Persistent ductus arteriosus	25	1	(4)
Atrioventricular canal defect	17	17	(100)
Fallot tetralogy	15	5	(33)
Transposition of great arteries	12	2	(17)
Aortic valve stenosis (AS)	9	3	(33)
Coarctation of aorta	6	0	(0)
Miscellaneous complex lesions	47	11	(23)
Total	320	80	(25)

TABLE 2. *Relative incidence of the major types of noncardiac defects.*

Types of defect	No.		%
Recognized syndrome			
Down	32		
Rubella	6		
Apert	2		
Williams	2		
Others	7		
Subtotal		49	54
Musculoskeletal		22	24.5
Neurological		8	9
Gastrointestinal		7	8
Urogenital		4	4.5
Total		90	100

Gastrointestinal defects were less common (7 cases) but tended to be severe. They included three cases of anorectal malformation, two of esophageal atresia and two of duodenal atresia. None of the patients had other features of the VACTERL association.[7]

Defects of the genitourinary system were few and comprised one case each of undescended testis, hypospadias, ambiguous external genitalia, and hydrometrocolpos with hydroureters and hydronephrosis.

Association Patterns

As stated earlier, 49 patients had recognized syndromes (Table 3). Sixteen (50%) of the 32 patients with Down syndrome had complete AV canal defect while 12 (37.5%) had either atrial or ventricular septal defect. Thus, 87.5% of patients with trisomy-21 had some form of intracardiac septal defect. The association is even more remarkable if patients with AV canal defect are considered as a group: 16 (94%) of 17 such patients had trisomy-21. Other syndromes encountered and the associated cardiac defects included: Holt-Oram (ventricular septal defect), scimitar (ventricular septal defect), Turner (pulmonary stenosis), Kartagener (situs inversus), and Noonan (Ebstein anomaly). One patient had asplenia syndrome. Apart from these recognized syndromes, there was no other clear association between the cardiac and noncardiac defects (Table 4).

Severity of the NCD

Table 5 shows the clinical grading of the NCD associated with each category of CHD. Sixteen (94%) of the 17 patients with AV canal defect had major NCD. Similarly, the incidence of major NCD was high in patients with complex cardiac lesions (82%), atrial septal defect (78%) and ventricular septal defect (58%). In all, the NCD were judged to be of minor clinical significance in 13 (16%) of the 80 affected patients, moderate in 11 (14%), and major in 56 (70%). This last group (of 56 patients) included all the patients with Down, Apert, rubella and Williams syndromes, as well as one two-month-old who presented with a small atrial septal defect and severe osteopetrosis complicated by optic atrophy, choanal atresia, and pancytopenia. Also included were the four patients with upper gastrointestinal tract obstruction and the infant who had hydrometrocolpos. All five patients had to undergo major noncardiac surgery in the newborn period.

Eight of the 80 patients in this series died, and in three, the NCD were thought to have been the sole or major cause of death. One was a neonate with a small atrial septal defect who died of massive hydrocephalus; the remaining two had scimitar syndrome and eventration of the diaphragm respectively. They both had trivial ventricular septal defect but succumbed to recurrent pulmonary infections.

TABLE 3. *Identified syndromes and associated cardiac defects.*

Syndromes				Associated Cardiac Defects				
(No. of Patients)		VSD	ASD	AV Canal defect	Fallot tetralogy	AS	PS	Miscellaneous/Others
Down	(32)	8	4	16	1	-	-	3
Rubella	(6)	4	1	-	-	-	1	-
Apert	(2)	2	-	-	-	-	-	-
Williams	(2)	-	-	-	-	2	-	-
Others	(7)	2	-	1	-	-	1	3

VSD=ventricular septal defect; ASD=atrial septal defect;AV=atrioventricular; AS=aortic valve stenosis; PS=pulmonary valve stenosis.

TABLE 4. *Types of noncardiac defects (NCD) with each form of congenital heart disease (CHD).*

	No. of	No. of		Type/Location of NCD (%)			
CHD	Patients	NCD	Syndrome	Neurological	Musculoskeletal	Gastrointestinal	Genitourinary
VSD	29	34	16 (47)	-	14 (41)	2 (6)	2 (6)
AV Canal defect	17	20	17 (85)	-	-	3 (15)	-
Miscellaneous complex lesion	11	15	6 (40)	3 (20)	2 (13.3)	2 (13.3)	2 (13.3)
ASD	9	9	5 (56)	1 (11)	3 (33)	-	-
Fallot tetralogy	5	5	1 (20)	2 (40)	2 (40)	-	-
Aortic valve stenosis	3	3	2 (67)	-	-	-	1 (33)
Pulmonary valve stenosis	2	3	2 (67)	1 (33)	-	-	-
Persistent ductus arteriosus	1	1	-	-	1 (100)	-	-

VSD=ventricular septal defect; AV=atrioventricular; ASD=atrial septal defect.

TABLE 5. *Clinical severity of the noncardiac defects, associated with each form of congenital heart disease (CHD).*

CHD	No. of Patients	Minor	Moderate	Major
VSD	29	8	4	17
AV canal defect	17	-	1	16
Miscellaneous complex lesions	11	-	2	9
ASD	9	2	-	7
Fallot tetralogy	5	1	2	2
Aortic valve stenosis	3	-	-	3
Pulmonary valve stenosis	3	-	2	1
Persistent ductus arteriosus	1	1	-	-
Transposition of great arteries	2	1	-	1

VSD=ventricular septal defect; AV=atrioventricular; ASD=atrial septal defect.

Discussion

Available reports suggest that the incidence of NCD in children with CHD varies quite considerably, depending on the study population and methodology. In general, the incidence rates are higher in autopsy than in clinical series.[8-12] Thus, the 25% incidence rate in our present clinical study is probably an underestimate. Yet even at that level, it is a disquietingly high rate; much higher indeed than the rates of 10% to 15% reported from other clinical studies in other countries.[9,11,12]

The question that immediately arises is whether the higher rate in our present study is a reflection of the general incidence of birth defects in the community or is the incidence high because our study population was composed of high risk patients who, since they already had one identified congenital defect, were likely to have a clustering of defects?

Published reports from other countries indicate that the incidence of birth defects in the general population varies between 1% and 10%[13-15] and that the rate rises about four- to tenfold in patients known to have CHD.[9,11] Comparable data from the Kingdom are scanty and emanated from studies on rather selected patient groups;[16,17] but they nonetheless suggest that congenital malformations are more common in Saudi newborns than in their British or American counterparts. In addition, observations in various pediatric units in the Kingdom also suggest that congenital malformations are a relatively frequent finding. Therefore, the 25% incidence in the present study may well be a reflection of both a relatively high general incidence and a clustering effect.

Down syndrome was the single most common associated defect in this study; it was present in 40% of the 80 patients and accounted for 35% of the 90 NCD. This finding has both etiological and clinical significance. First, it confirms the prime position of this chromosomal defect in the etiology of CHD. In other countries, Down syndrome accounts for about 5% of all CHD. [8,9,18-20] In our series, the corresponding figure is 10% and, as we indicated in our previous communication,[2] the excess seems to be attributable to advanced maternal age. This, then, is one area that deserves attention whenever prevention strategies are to be formulated.

Our findings again confirm the well-recognized association between Down syndrome and intracardiac septal defects.[11,21,22] The clinical implication is obvious: patients with Down phenotype should be carefully examined for CHD. In general, about 40% of them will be found to have a cardiac defect;[11,21] and there is an 87.5% probability that the defect will be located in the cardiac septa or endocardial cushion. An awareness of this association pattern should aid early detection of CHD in such patients and thus facilitate the timely formulation of a management plan, including surgical intervention where necessary.

Finally, we wish to draw attention to the high incidence of mental retardation in the patients we studied. In all, 48 patients, that is, 15% of the original 320 patients and 60% of the 80 with NCD, had varying degrees of mental retardation, 42 as part of syndrome complexes and six as isolated findings. This figure is uncomfortably high and becomes even more worrisome when it is appreciated that such mental defects may not be amenable to surgery. Thus, even after successful cardiac surgery, such NCD may turn out to be the major determinant of the quality of life. There is, therefore, a need for a national survey on birth defects, and if the relatively high figures obtained in this study are confirmed, appropriate prevention strategies will be indicated.

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PROFILE OF CANCER IN RIYADH ARMED FORCES HOSPITAL

Osama M. Koriech, MBBCh, DMRT, FRCR; Rashid Al-Kuhaymi, FRCS

The relative frequency of malignant disease varies with sex, age, race and geographic location. The frequency differs among the developed and developing countries. A review of the first 5000 histologically confirmed malignancies seen at the Riyadh Armed Forces Hospital Oncology Department confirmed differences from those encountered elsewhere. With the absence of a National Cancer Registry, only relative frequencies can be reported. In this series, gastrointestinal tract cancers were the most frequent, at nearly 18%, with high relative frequency of cancers of the liver and esophagus. Colorectal malignancies were less frequent than in the West. Lymphoma was the second most frequent malignancy at 13% with 2.5:1 ratio of non-Hodgkin lymphoma to Hodgkin disease. In both groups, poor prognostic histological varieties were more frequent than in the West. Breast cancer was the most frequent malignancy in females, accounting for 24% of all female cancers, in spite of the infrequency of the traditional risk factors of nulliparity, late age of first pregnancy, late age of menopause, and high dietary fat consumption. Two-thirds of patients with breast cancer were premenopausal. Other malignancies encountered at a higher frequency than in developed countries include hepatocellular carcinoma and nasopharyngeal cancer. This high relative frequency could be related to the high incidence of viral hepatitis and Epstein-Barr virus infections, respectively. The high relative frequency of oral cavity cancers is presumed to be due to chewing Qat and Shama. Thyroid cancer relative frequency was just over 5%, with a high predominance in females. No obvious etiological factors are identified. The relative frequency of bronchogenic cancer is low at 5%. This is likely to increase with the progressive rise in the habit of cigarette smoking. Skin cancer, on the other hand, is low, presumably due to the traditional dress covering the entire body and the head. *Ann Saudi Med 1994;14(3):187-194.*

The pattern of incidence and death rates of malignant disease vary with sex, age, race and geographic location with wide regional variations. Out of six million new cases of malignant disease diagnosed worldwide, every year over four million die of their disease. In contrast to developing countries, developed countries have a higher incidence, where deaths from cancer are exceeded only by those of cardiovascular disease. The incidence and frequency of cancer at different sites also fluctuate each decade. The steady rate of occurrence of the most commonly occurring cancers in the United States, as a model of Western culture, suggests effects of life-style and/or environmental factors acting over years or decades.[1]

The relative and real incidence of cancer in developing countries is likely to increase steadily over the next few generations. This is due to the reduction in the incidence of infectious and parasitic diseases and natal and perinatal mortality. As health services improve, the population average age will increase, thus potentially increasing the real incidence of malignant disease. The introduction of industrial carcinogens and "westernization" of social and dietary habits will increase the exposure to potentially carcinogenic agents, frequently without the necessary health and legal quality assurance controls.

Saudi Arabia is a vast and rapidly developing country with well-established health services expeditiously developed over the last two decades. Saudi Arabia occupies most of the Arabian peninsula and has widely varied environmental and geographical conditions and social habits. Marked variations in the relative frequency of cancer in different regions[2-4] are recognized. In common with most developing countries, there is not yet an established National Cancer Registry. Thus, most reports of the frequency of malignant disease may reflect referral pattern rather than the real incidence in the population.[5,6]

The Riyadh Armed Forces Hospital (RAFH) is a major referral hospital in this vast Kingdom. The Department of Oncology was established in 1981 with facilities in radiation therapy and chemotherapy. In this institution, oncology services have an open eligibility. The referral accordingly is not restricted to military personnel and/or their families.

Material and Methods

This study analyzes the first 5000 consecutive cases of malignant disease seen in the Oncology Department of the Riyadh Armed Forces Hospital. All patients were seen

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From the Departments of Oncology (Dr. Koriech) and Surgery (Dr. Kuhaymi), Riyadh Armed Forces Hospital, Riyadh.

Address reprint requests and correspondence to Dr. Koriech: Director, Department of Oncology, Riyadh Armed Forces Hospital, P.O. Box 7897, Riyadh 11159, Saudi Arabia.

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after substantiating the diagnosis histologically in our institution.

Results

Of the 5000 patients, there were 2940 males and 2060 females, with a ratio of 1.4:1. The median age for the whole population was 46 years, and for males and females was 49 and 43 years, respectively. Patients over 65 years of age accounted for 16% of patients.

The spectrum of malignant disease in Saudi Arabia varies, as expected, according to age. In children, acute leukemia accounted for 34%, central nervous system tumors 24%, lymphomas 18% and Wilms' tumor in 11% of all cancers. The most common cancers over the age of 65 were those of gastrointestinal tract cancers, accounting for 32%, with colorectal cancers accounting for 13% of all cancers. Hepatocellular carcinoma was noted in 12%, esophageal carcinoma in 10% and bronchogenic carcinoma in 9%. Genitourinary tract cancer accounted for 13% with prostatic cancers responsible for under 6% of this age group.

The frequency and the ranking of the different types of malignancies for the overall male and female populations are as shown in Tables 1, 2 and 3. Overall, gastrointestinal tract malignancies were the most frequent, followed by lymphoma, head and neck, and breast cancers.

Primary malignant tumors of the digestive organs, excluding lymphomas, formed 18% of all cancers and were the most frequent sites in males, accounting for approximately 21.5%. In females, they were the second most frequent, after breast cancer, accounting for nearly 13%. The male to female ratio was 2.4:1. The site distribution according to sex is shown in Tables 4, 5, and 6. In common with other developing countries, cancer of the liver was high at 6% of all cancers with a male to female ratio of 4:1 in this series. This was followed by cancer of the esophagus, accounting for 4% of all malignancies seen. On the other hand, the overall relative frequency of colorectal cancers was low at 3%.

Breast cancer was the most frequent malignancy in females, accounting for over 24% of all female cancers. The median age of Saudi patients with breast cancer was 44 years, about one decade younger than their Western counterparts. Patients under the age of 50 constituted 64% of all breast cancer patients. About 2% of patients seen were males.

Malignant lymphoma in Saudi Arabia accounted for approximately 13% of all cancers. It is exceeded only by gastrointestinal tract cancers in males and by breast and gastrointestinal tract cancers in females. The male to female ratio is 1.8:1. The overall median age was 35 years. The median age for males was 34 years and for females, 39 years.

TABLE 1. *Overall distribution and ranking.*

Malignancy	Number	Percentage (%)
Gastrointestinal	909	18
Lymphoma	660	13
Head and neck	497	10
Breast	465	9
Nervous system	410	8
Genitourinary	371	7
Leukemia	294	6
Sarcoma	281	6
Endocrine	250	5
Respiratory	239	5
Gynecologic	192	4
Unknown primary	153	3
Skin	85	2
Others	194	4
Total	5000	

TABLE 2. *Distribution and ranking of malignant diseases in males.*

Malignancy	Number	Percentage (%)
Gastrointestinal	639	22
Lymphoma	426	14
Head and neck	370	13
Genitourinary	317	11
Nervous system	274	9
Respiratory	192	7
Leukemia	187	6
Sarcoma	182	6
Unknown primary	101	3
Endocrine	71	2
Skin	55	2
Multiple myeloma	48	2
Others	78	2
Total	2940	

TABLE 3. *Distribution and ranking of malignant diseases in females.*

Malignancy	Number	Percentage (%)
Breast	457	22
Gastrointestinal	270	13
Lymphoma	234	11
Gynecology	192	9
Endocrinology	179	9
Nervous system	136	7
Head and neck	127	6
Leukemia	107	5
Sarcoma	99	5
Genitourinary	54	3
Unknown primary	52	3
Respiratory	47	2
Others	106	5
Total	2060	

The median age for non-Hodgkin lymphoma was 46 years. There was a higher frequency of unfavorable histological types than in the West. The favorable nodular forms are infrequent. Only 5% of all non-Hodgkin lymphoma were of low-grade histological variety, while 49% were intermediate grade and 46% high-grade histological varieties. Most patients presented at an advanced stage. Primary sites of non-Hodgkin lymphoma varied considerably from those in the West. Over 56% of our patients presented with extranodal disease, with primary gastrointestinal lymphoma accounting for over 46% of the extranodal group.

Hodgkin disease is less common at 4% than non-Hodgkin lymphoma at 9% with a ratio of 1:2.2. Males predominate with a sex ratio of 2.2:1. The overall median age was 27 years. Median age for males was 29 years and for females, 23 years. Poor histological types are more frequent in this series than in the West. Histologically, the mixed cellularity type is the most common in the Saudi patients, constituting 55% of all Hodgkin disease cases seen. Conversely, the nodular sclerosis type, most common in Western countries, forms 29% of cases. The least frequent histological variety was the lymphocytic predominant type accounting for only 4% of patients.

Burkitt lymphoma accounted for only 5% of all lymphomas with a median age of six years. Patients were mostly referred from the Gizan area, a southern mountainous and rainy region, with a high incidence of malaria. Unlike the African variety, most cases presented initially with intra-abdominal disease with subsequent high incidence of central nervous system involvement.

TABLE 4. *Overall distribution of gastrointestinal tract malignancies.*

Malignancy	Number	Percentage (%)
Liver	293	32
Esophagus	207	23
Bowel	160	18
Stomach	120	13
Pancreas	66	7
Biliary tract	59	6
Others	4	<1
Total	909	

TABLE 5. *Distribution of gastrointestinal tract malignancies in males.*

Malignancy	Number	Percentage (%)
Liver	239	37
Esophagus	132	21
Bowel	107	17
Stomach	94	15
Pancreas	44	7
Biliary tract	21	3
Others	2	<1
Total	639	

TABLE 6. *Distribution of gastrointestinal tract malignancies in females.*

Malignancy	Number	Percentage (%)
Esophagus	75	28
Liver	54	20
Bowel	53	20
Biliary tract	38	14
Stomach	26	10
Pancreas	22	8
Others	2	<1
Total	270	

TABLE 7. *Primary sites of head and neck cancers.*

Primary Sites	Number	Percentage (%)
Nasopharynx	206	41
Oral cavity	121	24
Larynx	74	15
Salivary	30	6
Oro- and laryngopharynx	25	5
Sinuses	19	4
Ear	11	2
Conjunctiva	6	1
Nasal cavity	5	1
Total	497	

The frequency of head and neck cancer in this series was approximately 10%. The site distribution of different head and neck cancers is presented in Table 7. The most common tumors are those of nasopharynx, oral cavity and larynx. Nasopharyngeal carcinoma accounted for just over 4% of all cancers. Male to female ratio was 4:1. The overall median age was 43 years, with a male median age of 45 years and female median age of 38 years with a predominance of poorly differentiated squamous cell carcinoma histology. Over 90% of patients presented with advanced stage T3-T4 and/or N2-N3 disease.

Carcinomas of the oral cavity, on the other hand, accounted for 2.5% of all cancers. Most patients are referred from the Gizan area in the southern region of the Kingdom, where chewing Qat and Shama is illegal but still habitual. The median age for oral cancers was 54 years. The primary sites are located in the tongue in approximately half of patients and in the floor of the mouth, gums and palate in the remaining half.

Excluding thyroid lymphoma, thyroid cancer is more frequent in this series than in the West. It accounted for 5% of patients, showing a female to male predominance of 2.4:1. The median age was 36 years. Most patients present with a thyroid swelling with or without a lymph node enlargement. Thyroid cancer in Saudi Arabia was peculiar with the infrequency of anaplastic variety. Papillary adenocarcinoma was present in 58%, follicular in 22%, mixed papillary and follicular in 8%, and anaplastic in only 6% of all cases. Medullary carcinoma was diagnosed in

3% of patients. Sarcoma and squamous cell carcinoma accounted for the remaining 3%.

In this series, cancer of the uterine cervix accounted for only 3%, while gestational trophoblastic tumors were noted in just over 1% of female cancers.

Prostatic cancer, a common neoplasm encountered in old age in developed countries, accounted for only over 2% of all male cancers. Bladder cancer was more frequent at 3% with a male to female ratio of 6.5:1. The median age is 67 years.

In this series, bronchogenic carcinoma accounted for a mere 5% of all cancers, ranking as the tenth most common malignancy. The median age of Saudi patients was 57 years, with marked male predominance of 4.3:1. It accounted for 6.5% of male cancers and ranked seventh. In females, it accounted for 2% of all cancers and ranked eleventh.

Skin cancer was rare, accounting for only 3% of all cancers. The male to female ratio was 2.2:1. Histologically, basal cell carcinoma was the most frequent, followed by squamous cell carcinoma, Kaposi sarcoma and melanoma.

Discussion

The study of incidence and distribution of cancer in certain populations helps in identifying possible causes that might be used as preventive tools. Prevention deals with avoiding or modifying exposures to factors that cause disease.[7] In the absence of a National Cancer Registry and the unavailability of mortality data in most if not all developing countries, the incidence is expressed only in relative frequencies. Relative frequency represents the percentage of a specific type of neoplasm in comparison to the overall consecutive cases of cancers seen over a specified period of time. Hospital-based data are usually presented in this manner. Unavoidable bias as a result of facilities available, special interests or referral trends will occur. Some types of cancer may be overrepresented and others may be underrepresented. Bias in reporting of cases from referral centers, such as in this series, is unavoidable, though it is the best possible representation of the extent and pattern of the cancer problem under these circumstances. The value of age standardization is limited by the absence of population data. The merits of studying the prevalence rate of different malignancies in different population groups will also be restricted.

In spite of these difficulties, important data can be identified. Overall pattern, temporal variations, and possible risk factors can be determined from such studies.

We believe that the following analysis has a small selection bias since the material was referred by all specialties. It could reflect a well-balanced representation of the different tumor sites in the Kingdom.

In common with other developing countries, Saudi Arabia is characterized by the relatively young age structure of its population. The overall median age of oncology patients is about one decade younger than Western patients, and agrees with that seen in other developing countries. Population under the age of 15 accounts for over 44% of individuals. This broad base of the population pyramid is produced by the high natural population growth and may account for the relatively lower incidence of epithelial cancers.

The real incidence of cancer is likely to increase as a result of the aging of this population and the unavoidable introduction of industrial and environmental carcinogens. The number of patients reported to cancer registries will also increase as health services improve and cancer detection and awareness of the public increases.

The profile of cancer in the Saudi population has some features in common with developing countries in addition to some specific features of its own. Similarities to the pattern in developing countries include the infrequency of bronchogenic and prostatic cancer. Bronchogenic cancer is a tumor related to heavy smoking and prostatic cancer increases with the aging of population. The high relative frequency of liver carcinoma is directly related to the endemicity of hepatitis B and possibly hepatitis C viral infections. Other epidemiological features of cancer incidence that are peculiar to the Saudi patients are the high frequency of lymphomas and nasopharyngeal, thyroid and esophageal cancers. These cancers are known to have wide regional variations in developing countries.

Sex and Age Distribution

In this series, the male to female ratio was 1.4:1. Though males constituted 45% of the population, they accounted for 59% of malignant disease seen. A similar observation has been reported from Egypt.[8] In the USA, the male to female ratio is 1:1.

In developed countries, elderly age groups constitute a large sector of the population. In the USA, cancer is predominantly a disease of old age; 58% of all new cancer cases and 66% of all cancer deaths occur in the 12% of the population over 65 years of age. This confirms the established relationship of age and cancer in this population. In this age group, the most frequently encountered tumors in American males are gastrointestinal cancer at 30% and prostatic cancer at 25% to 33%, whereas in females, gastrointestinal at 40% and breast cancer at 20% predominate.

In this series, as seen elsewhere, there was a higher relative frequency of malignancies in older age groups. Patients over the age of 65 accounted for 16% of all cancers though representing only 2.5% of the population. It was noteworthy to observe that the most common cancers are those of the gastrointestinal tract, with the relative frequency of colorectal cancers less than in the West.

In this series, the overall median age was 46 years. The median age was higher in males at 49 than in females at 42 years. This is approximately a decade younger than Western patients, though similar to that encountered in the developing world. This could be partly accounted for by the young population distribution, the predominance of environmental factors such as infections, poor hygienic conditions and the nonconformity to industrial regulations controlling the emission of carcinogens into the environment.

Gastrointestinal Tract Cancers

The pattern of gastrointestinal tract cancers varies in Saudi Arabia more than in the West.[9] It has, in common with developing countries, the high incidence of hepatocellular carcinoma and the less frequent colorectal cancers. On the other hand, a peculiarity of cancer in Saudi Arabia is the high relative frequency of esophageal cancer.

The endemicity of hepatitis viral infection in the developing world is well recognized. The highest rates of hepatocellular carcinoma have been reported from sub-Saharan Africa, China and Southeast Asia, reaching epidemic proportions in these developing countries.[10] The etiology is related to hepatitis-B virus infection, with aflatoxin as a possible co-factor. The incidence of hepatitis-B viral antibody titer in Saudi Arabia was reported as high as 60%,[11] while the incidence of hepatitis-B antigen titer in the population at large is approximately 5%. Hepatitis-B virus vaccination program for children in an attempt to reduce the incidence of hepatitis-B infection is underway with encouraging early results. Long-term implications of this program and its influence on the development of hepatocellular carcinoma remain to be seen.

The esophageal cancer belt extends from Russia and Northern Iran to East China. Low socioeconomic conditions and exposure to nitrosamine are possible etiologic factors. The high frequency of esophageal cancer in France and Switzerland is related to high alcohol consumption and smoking. Carcinoma of the esophagus was the second most common among the gastrointestinal tract cancers in Saudi Arabia. Though the incidence is less frequent than in the Caspian Sea littoral area, it is higher than in the West. The area of high relative incidence of esophageal cancer in the central region of Qassim remains unexplained, though environmental factors are the most likely and need to be explored. Many patients reported consumption of thermally hot food. Nitrite pollution of the soil and drinking water remains to be explored. Risk factors identified elsewhere such as alcohol and opium are not encountered in this strictly Moslem society. Asymptomatic chronic esophagitis, probably a precancerous lesion in high risk areas, has not been reported in Qassim or elsewhere in the Kingdom.

Colorectal cancers, on the other hand, are less frequent in Saudi Arabia than in the West.[12,13] This could be due to the difference in the dietary habits between the two cultures. Possible etiologic factors for the high incidence in the West include high fat diet, high fecal steroids, low fiber diet and change in fecal microflora. The Arabian culture diet, until recently, contained high levels of fiber and lower levels of fat and protein, though this appears to be slowly changing.

Malignant Lymphoma

Malignant lymphomas are relatively common in countries of the Middle East. In addition to Saudi Arabia,[6] they are common in Egypt, accounting for 10%, and Iraq 9.5% of all cancers. Low socioeconomic status, malnutrition, and the prevalence of parasitic and viral infections have been associated with the development of lymphomas.

The high ratio of lymphoma to leukemia of 2.2:1 is consistent with the pattern observed in developing countries and is the reverse of that reported from the Western world. The high level of Epstein-Barr viral infections acquired in childhood in developing countries might be an important etiological factor.

Study of non-Hodgkin lymphoma in this series indicates that intermediate and high-grade histological varieties are more frequent in Saudi Arabia than in Western patients. Follicular lymphomas are infrequent at 5% in comparison to nearly 40% of all lymphomas in Western reports.[14]

Burkitt lymphoma is an undifferentiated non-Hodgkin lymphoma predominant in Africa where it affects mostly facial bones. It has a different clinical pattern in Saudi Arabia. It is of intermediate frequency between the very low incidence in the West and the high incidence in Africa. In Saudi Arabia, it arises mostly from the abdomen and frequently involves the central nervous system. Nonetheless, it has in common with the African variety the feature of presenting in mountainous rainy areas with a high incidence of malaria in the southern region of Saudi Arabia. The relationship to Epstein-Barr virus cannot be confirmed as yet, though is probable.

Mediterranean lymphoma or immunoproliferative small intestinal disease (IPSID) is uncommon in Saudi Arabia. It was reported in the Middle East from Saudi Arabia, the Gaza Strip, Iran, Lebanon, Tunisia, Algeria, and Egypt.[15] It is characterized by a preneoplastic inflammatory stage of the stomach and the full length of the small intestinal mucosa, associated with diarrhea and malabsorption. The improved socioeconomic development might be responsible for the low incidence in Saudi Arabia, as it is a disease of low socioeconomic status. Alpha-heavy chain proteins may be demonstrated in plasma and in immunohistochemical studies of tumor cells.

A further significant clinical finding is the high incidence of endemic splenomegaly in the southern region of Saudi Arabia. This can delay the diagnosis of the more frequent intra-abdominal lymphoma and disrupts clinical staging.

Head and Neck Cancer

Epithelial head and neck cancers have significant differences in etiology, natural history, therapeutic modalities and responses among the distinct primary sites. They are reported together due to their epithelial origin and the infrequency of varying sites in Western practice. In this series, epithelial head and neck cancers accounted for 10% of all cancers.

Cancer of the nasopharynx is most frequently found in Singapore, Southern China and Hong Kong. Medium risk areas include Tunisia and Morocco with a relative frequency between the high incidence of the East and the low incidence of the West. Thus, Saudi Arabia, at a relative frequency of 4%, is a medium risk area. The high frequency in males and the poorly differentiated histology are features seen in endemic regions. It is frequently associated with Epstein-Barr virus infection. Epstein-Barr viral titers were not routinely or consistently examined in this series. The relationship to Epstein-Barr virus is not yet confirmed in Saudi Arabia.

Oral cavity cancers in Saudi Arabia, on the other hand, are mostly referred from the southern regions of the Kingdom. The frequency is lower than in India and Pakistan but higher than Western countries. In India, chewing betel mixture is assumed to be the most important etiologic factor. The chewing of the tobacco-like substances, Shamma and Qat, in the southern region of Gizan and neighboring Yemen, may contribute to the high frequency of oral cancer in these regions.

Cancer of the lip is rare, presumably due to the rarity of cigar and pipe smoking, though referral pattern might be a factor, as most patients would have a surgically resectable disease, not requiring a referral to specialized oncology services.

Breast Cancer

Breast cancer is the most common female cancer in North America and Europe. Risk factors include family history, nulliparity, late age of first pregnancy, late age of menopause, high socioeconomic status, and low breast feeding habit. Obesity and high dietary fat consumption as well as family history are also significant risk factors for breast cancer.[16] It is possible that an unidentified endocrine profile is associated with increased risk, and it may be that dietary fat plays a role, possibly altering the patient hormonal profile.

The mean age of menarche in Saudi Arabia is 11 and the mean age of menopause is 48 years. Nulliparity is rare in this society, where the fertility rate is 7.2 pregnancies per female. Most women, if not all, would breast feed their offspring up to two years and certainly not less than one year. Family history is so far inconsequential. Thus, most of the classic risk factors involved in the development of breast cancer in the West are not necessarily significant or their contribution to the cancer incidence is not confirmed in this population.

As the breast is considered a hormone-dependent organ, estrogenic stimulation in the presence of progesterone deficiency might induce breast cancer.[17] At this stage of social development, approximately 30% of females use oral contraceptive pills at some stage of their life. It is anticipated that this incidence and duration of use will increase over the next generations.

Though it remains controversial, data suggests that breast cancer in premenopausal patients may be biologically more aggressive than in postmenopausal patients. Breast cancer in Egypt, with population and breast cancer characteristics comparable to those in Saudi Arabia, is said to be more aggressive than that encountered in Western patients.[18] This was explained partly by the predominance of premenopausal patients, a finding comparable to that seen in this series. In common with Egypt and other developing countries, most patients present with an advanced stage and would have a poor long-term response.

In this series, there is a high relative frequency of breast cancer in males. Though there are no recognized etiological factors, the high incidence of liver cirrhosis caused by hepatitis-B viral infection might cause hyperestrinism that induces malignancy in susceptible male patients.

Female Genital Organs

In spite of early marriage and multiparity, cancer of the cervix is rare in Saudi Arabia, contrary to the high frequency of this tumor in other developing countries. The high incidence of cervical cancer in Lebanon, Morocco and Tunisia is possibly related to increased exposure of population to human papilloma virus infection. Male circumcision and the high level of genital hygiene in the Saudi population may account for this low frequency. On the other hand, gestational trophoblastic tumors were more frequent than in the West. This is in common with most of the developing world.

Male Genital Organs

Prostatic carcinoma affects mainly elderly patients, with a median age in the USA of 66 years. The low relative frequency in Saudi Arabia may be related to the population age distribution though racial, social, sexual or environmental factors cannot be excluded. The median age in this series, though, is comparable to that in the West.

Bladder Cancer

Cancer of the bladder is common in Egypt, where it is related to bilharziasis. Chronic bacterial infection, associated with bilharziasis, plays a major role in bladder carcinogenesis.[19] It is usually squamous cell variety. The non-bilharzial transitional bladder cancer is most common in the USA, where tobacco smoking and industrial chemicals are important risk factors. In contrast to squamous cell bladder cancer in Egypt, bladder cancer is less frequent in Saudi Arabia and is mostly of transitional cell histology. In Saudi Arabia, bilharziasis is seen in the southern Gizan region of Saudi Arabia and neighboring Yemen. Most bladder cancer cases are referred from this region. Most cases present at an advanced stage with male predominance. Cancer of the penis is, as expected, rare in view of the traditional male circumcision. There is, nonetheless, the rare incidence of penile shaft malignancy following pubic circumcision.[20]

Thyroid Cancer

Thyroid cancer is a rare tumor worldwide. Areas of high incidence in Iceland and Japan are known. Risk factors include exposure to irradiation in childhood and low iodine level. Thyroid cancer frequency in Saudi Arabia appears to be unexpectedly high.[21] The population does not seem to have been exposed to radiation during childhood. Background irradiation level is not known. Possible factors might include iodine deficiency, particularly in this vast desert land, though there is no reported untoward rise in goiter.

Bronchogenic carcinoma

Over 80% of lung cancer is due to tobacco smoking. In developed countries, lung cancer is the most frequent oncologic problem. The low incidence in Saudi Arabia is probably due to the relatively low incidence of cigarette smoking. Unfortunately, this injurious and antisocial habit is increasing in this newly developing society. Lung cancer in Kuwait accounts for over 20% of male cancers and 7.5% of female cancers. Kuwait is known to have started on the path of smoking decades before Saudi Arabia. In the United States and Europe, there has been a striking increase in the incidence of lung cancer, particularly in females. The incidence of lung cancer in Saudi Arabia and other developing countries is likely to show a comparable or even faster increase over the next few decades due to the rise in the habit of cigarette smoking.

Skin Cancer

Worldwide, the highest rate for skin cancer was reported in Northern Australia. It is associated with exposure of the white-skinned population to intense ultraviolet rays of the sun. In the Middle East, skin cancer is particularly common in Iran, but rare in Egypt and Saudi Arabia. The relative frequency of epithelial skin cancer in Saudi Arabia is of some interest, due to the high intensity of the sun and the high level of ultraviolet-B rays. In Saudi Arabia, skin protection with the traditional dress and head gear and the dark complexion of the skin may account for the low incidence. Ethnic susceptibility, on the other hand, cannot be excluded. Kaposi sarcoma relative frequency was higher than in the West. With one exception, a blood transfusion-related HIV infection, all cases with Kaposi sarcoma seen were non-AIDS related.

The profile of cancer in Saudi Arabia, as well as other developing countries, has common features that may account for the cancer distribution seen. The high incidence of viral infections such as hepatitis-B and C infections, parasitic, and bacterial diseases as well as frequent nutritional problems and natural environmental factors, such as vast desert areas with heavy solar exposure, might play an important role in the etiology of certain malignant tumors. The recent development of rapid industrialization and urbanization may lead to increased exposure of population to potent chemocarcinogens and alter the present cancer pattern over the next few generations.

In common with other developing countries, a large portion of the population is young. Young age groups have a low incidence of epithelial malignant disease and a higher incidence of lymphomas, sarcomas and other non-epithelial cancers. The recent improvement in health services and the curability of infectious diseases will lead to aging of the population and consequently to an increase in the absolute incidence of malignant disease as well as a change in the pattern of cancers seen.

The development of a National Cancer Registry, still lacking in this rapidly developing Kingdom, is necessary. The data collected are necessary in planning health care facilities and research programs. El-Bolkaini [8] confirms the importance for developing countries to set up cancer control programs, to include research into etiological factors and the active development of preventive strategies, as well as proper planning of cancer treatment services. The need for such a program in Saudi Arabia cannot be overemphasized.

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GASTRIC CANCER IN SOUTHERN SAUDI ARABIA

Jamal Hamdi, FRCS; Nader A. Morad, FCAP

A total of 84 cases of primary gastric cancer were diagnosed in the histopathology laboratory of Asir Central Hospital over a five year period (1987 to 1991). Seventy-two patients (86%) were Saudis and 12 cases (14%) were non-Saudis. The mean age of the patients included in this study was 60 years with a range of 22 to 85 years and a male:female ratio of 4.6:1. Intestinal adenocarcinoma occurred in 63 patients (75%) followed by malignant lymphomas in 12 cases (14%) and diffuse adenocarcinoma in nine cases (11%). The gastric antrum was the most common site affected (47%), followed by gastric corpus (27%), cardia (14%), and fundus (12%). Comparisons of our findings to similar reports from other provinces of Saudi Arabia and other countries are discussed. *Ann Saudi Med 1994;14(3):195-197.*

Gastric cancer is a leading cause of death worldwide.[1] Variations in the pattern of gastric cancer exist between developed countries and developing countries.[2] Environmental as well as genetic and racial factors play an important role in the causation of gastric cancer.[3] Comparative studies of the pattern of gastric cancer in various populations might help in better understanding of environmental and genetic or racial factors contributing to the evolution of gastric cancer.

Several reports from the Kingdom of Saudi Arabia have recently studied general patterns of cancer,[4-6] and patterns of gastrointestinal tract malignancies.[7-9] Only a few reports have been devoted to the study of the pattern of gastric cancer.[10] The current study describes the general pattern of primary gastric cancer in Southern Saudi Arabia for the first time. Our findings of patients' age, sex, nationality, location, and histological type of gastric cancer are compared to findings from other provinces of the Kingdom as well as from other countries.

Patients and Methods

The current study included 84 cases of primary gastric malignancy diagnosed at Asir Central Hospital during a five year period (1987 to 1991). Diagnosis of cancer was made histologically in all 84 cases (34 cases had gastrectomy and in the remaining 50 cases, the diagnosis was made in endoscopic biopsies only). All specimens were fixed in 10% formalin and stained with hematoxylin and eosin (H&E). Special stains including immunohistochemical markers were done when needed. Classification of gastric carcinoma into intestinal and diffuse type was made according to the criteria of Lauren.[11] All cases of malignant lymphoma were primary gastric lymphoma as the patients did not have disseminated disease at the time of presentation, no generalized lymphadenopathy, negative bone marrow biopsies and no internal lymphadenopathy by computed tomography (CT) scanning and x-rays of the chest, abdomen and pelvis. The medical records and endoscopy reports were reviewed to identify the patients' age, sex, nationality and location of the tumor. The location of the tumor was defined as the part of the stomach containing the major portion of the tumor. The latter was assessed pathologically in 34 resected specimens and endoscopically in the remaining 50 cases. These 50 cases were either referred to other institutions for further therapy or were lost to follow-up. In order to evaluate our confidence in histological classification of adenocarcinoma in endoscopic biopsies, we have independently reviewed the endoscopic biopsies of the 34 cases that have undergone subsequent gastrectomy and tumor typing in biopsies and gastrectomy specimens were compared. The data analysis included the patients' age, sex, nationality, endoscopic and/or pathologic location of the tumor, and their histological types. Our data are expressed in total absolute numbers and/or percentage (crude relative) frequencies.

Results

Distribution of various histological types of gastric cancer according to age, sex, and nationality is shown in Table 1. A total of 75% of our 84 patients had intestinal adenocarcinoma, 14% had primary non-Hodgkin malignant lymphoma (NHL) of the stomach and the remaining nine patients (11%) had diffuse gastric adenocarcinoma. The latter classification of adenocarcinoma into intestinal and diffuse type was made according to the histologic criteria

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From the Departments of Pathology (Dr. Morad) and Surgery (Dr. Hamdi), King Saud University, College of Medicine, Abha Branch, Abha.

Address reprint requests and correspondence to Dr. Hamdi: Department of Surgery, King Saud University, Abha Branch, College of Medicine, Abha Branch, P.O. Box 641, Abha, Saudi Arabia.

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set by Lauren.[11] Mean age of intestinal adenocarcinoma cases was 64 years compared to 55 and 58 years for diffuse adenocarcinoma and gastric NHL respectively. The male:female ratio was 4.6:1, 4.7:1, 3:1 and 8:1 for all cases of intestinal adenocarcinoma, NHL and diffuse adenocarcinoma respectively. The Saudi:non-Saudi ratio was 6:1, 11.6:1 and 1.25:1 in all cases of intestinal adenocarcinoma, NHL and diffuse adenocarcinoma respectively. All 24 cases of intestinal adenocarcinoma were correctly diagnosed in pregastrectomy endoscopic biopsies when compared to diagnosis in gastrectomy specimens. One case diagnosed in biopsy as intestinal adenocarcinoma turned out to be of the diffuse type in subsequent gastrectomy. Six diffuse adenocarcinomas and three NHL cases were correctly diagnosed in endoscopic biopsies when compared to diagnosis in gastrectomy specimens. Grading of 24 intestinal adenocarcinoma cases diagnosed in gastrectomy specimens was: one case of well differentiated, 18 cases of moderately differentiated, and five cases of poorly differentiated. None of the 31 cases of adenocarcinoma diagnosed in gastrectomy specimens were of early gastric cancer type.

Table 2 shows the distribution of various histologic types of gastric cancer according to the gastric site affected. Forty-seven percent of all cancer cases occurred in the gastric antrum, which was also the most common location of intestinal adenocarcinoma. The antrum was affected in only 33% of cases of diffuse adenocarcinoma and NHL.

Discussion

The general pattern of cancer and pattern of primary gastrointestinal tract cancer in Asir Province have been recently published.[12,13] Gastric cancer is the fifth ranking type of cancer in the Asir region, representing 6.7% of all cancer cases. Gastric cancer represented 27% of primary gastrointestinal tract cancer cases with gastric to colorectal cancer ratio of 1.3:1. In developed countries, colorectal cancer accounts for more than 75% of primary gastrointestinal tract cancer compared to only 10% for gastric malignancy.

Features of gastric cancer among our patients are similar to features reported from high risk areas worldwide.[14-16] These include median age in the seventh decade (60 years), males more frequently affected than females (4.6:1), intestinal type adenocarcinoma more common than diffuse type (7:1) and distal location is more frequent than proximal location (1.8:1). Non-Hodgkin malignant lymphoma of the stomach represented 14% of our patients, whereas in Western countries, NHL represents only 2% to 5% of gastric malignancy.[17] In a recent study from the Riyadh area, NHL represented 22% of all gastric cancer cases.[10]

Features of gastric adenocarcinoma in our patients are significantly different when compared to the Riyadh study[10] regarding patients' nationality, histopathologic types, tumor location, sex, and age. In our study, the ratio of Saudis:non-Saudis was 7:1 compared to 1.75:1 in the Riyadh area, and the ratio of intestinal type: diffuse adenocarcinoma among our Saudi patients was 11.6:1 compared to a ratio of 1.8:1 among Saudi patients from the Riyadh area. Distal (antral) intestinal adenocarcinoma was seen in 51% of our cases compared to only 23% of the patients from the Riyadh area. Mean age of our cases with intestinal adenocarcinoma was 64 years compared to

TABLE 1. *Distribution of various histopathologic types of gastric cancer according to age, nationality and sex.*

	Age (years)		Nationality		Sex		
Histopathologic diagnosis	Mean	Range	Saudi	Non-Saudi	Male	Female	Total Number of Cases
Intestinal type adenocarcinoma	64	25-85	58 (92)	5 (8)	52 (83)	11 (17)	63 (75)
Diffuse type adenocarcinoma	55	28-75	5 (55.5)	4 (44.5)	8 (89)	1 (11)	9 (11)
Malignant lymphoma	58	22-80	9 (75)	3 (25)	9 (75)	3 (25)	12 (14)
Total	60	22-85	72 (86)	12 (14)	69 (82)	15 (18)	84 (100)

( )=numbers in parenthesis are percentage (crude relative) frequencies.

TABLE 2. *Distribution of various histologic types of gastric cancer according to gastric* sites affected.*

Histopathologic type	Cardia	Fundas	Body	Antrum	Total
Adenocarcinoma "Intestinal type"	11 (17)	7 (11)	13 (21)	32 (51)	63 (100)
Adenocarcinoma "Diffuse type"	1 (11)	2 (23)	3 (33)	3 (33)	9 (100)
Malignant lymphoma	-	1 (8)	7 (59)	4 (33)	12 (100)
Total	12 (14)	10 (12)	23 (27)	39 (47)	84 (100)

*=gastric site affected was identified grossly considering the location of the major portion of the tumor during gross pathologic examination of the resected stomach and/or endoscopy.

55.6 years in the Riyadh area. In our study, diffuse adenocarcinoma was eightfold higher in males compared to females, whereas in the Riyadh area, this ratio was 2.5:1.

In Western countries where the incidence of gastric cancer is declining, the patient's age, the male:female ratio, the intestinal:diffuse adenocarcinoma ratio and the distal:proximal tumor location ratio of gastric carcinoma have all decreased.[18-21] This trend is noted in Saudi patients from the Riyadh area but not in our Saudi patients. In our study, Saudi patients represented 92% of intestinal and 55% of diffuse gastric adenocarcinoma whereas in the Riyadh area, Saudi nationals represented 50% and 86% of intestinal and diffuse adenocarcinoma respectively. Furthermore, Saudis represented 88% of our gastric adenocarcinoma cases compared to 62% in the Riyadh study. Features of gastric carcinoma in our Saudi patients are similar to those reported among high risk populations worldwide. Our speculations are that factors responsible for the decline of gastric cancer in Western countries are operating in the Riyadh area but are not operating in Asir Province. These factors include dietary habits, socioeconomic status, and the presence of *Helicobacter pylori* associated gastritis.[22-24]

In conclusion, our study has described for the first time the general pattern of gastric cancer in Southern Saudi Arabia with features comparable to those seen in high risk populations worldwide.[14-16] Significant differences were seen when our results were compared to those recently reported from the Riyadh area.[10] Similar differences were noted in countries where the incidence of gastric cancer has declined. These differences should be further investigated considering various geographical and demographical features of different provinces of the Kingdom of Saudi Arabia.

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MALIGNANT CYSTOSARCOMA PHYLLODES: A REVIEW OF THE CLINICAL EXPERIENCE AT KING FAISAL SPECIALIST HOSPITAL AND RESEARCH CENTRE

Adnan Ezzat, MBBCh, FRCPC; Abdulmajeed Abdulkareem, MD, FRCS(C), FICS;
Mohammad El-Senoussi, MD; Rafal Wierzbicki, MD, FRCPC;
Shouki Bazarbashi, MD; Bashir Ahmed Khan, PhD; Ahmed Abdel-Warith, MD

Twelve females with cystosarcoma phyllodes of the breast were referred to King Faisal Specialist Hospital and Research Centre (KFSH&RC) between 1980 and 1990, representing 0.8% of breast cancer patients seen during this period. Median age was 45 years (range 16 to 65 years). Seven patients (58%) were premenopausal. All patients presented with breast mass, which measured >10 cm in 58% of them. The median duration of symptoms was 15 months (range two to 174). Neither axillary lymph nodes nor distant metastases were seen at presentation. Surgery was the cornerstone of primary treatment (wide local excision in three and mastectomy in nine). Two patients received adjuvant chemotherapy and locoregional irradiation. All patients had malignant tumors histologically. Of the four tumors assayed for hormonal receptors, one was positive for estrogen and progesterone receptors. At a median follow-up of 17 months (range two to 77), four patients had relapsed; one died at 19 months and the projected five year survival is 83%. This limited data supports the observation that malignant cystosarcoma phyllodes is a distinctive clinicopathological entity of female breast cancer with a different natural history from carcinoma of the breast. Our survival results are similar to reported experience from the literature. *Ann Saudi Med 1994;14(3):198-200.*

Cystosarcoma phyllodes is an uncommon distinctive fibroepithelial tumor of the breast without counterpart in any other organ.[1] It constitutes less than 1% of all malignant breast tumors.[2] It is a peculiar tumor that produces a spectrum of diseases ranging from benign, yet with the risk of local recurrence, to intermediate (borderline), to malignant, sometimes with a rapidly progressive course. Since it was originally described by Johannes Muller in 1838,[3] controversies concerning nomenclature, histologic interpretation, prediction of cytologic behavior and prognostic indices of this disease remain unresolved. Although surgery remains the cornerstone of primary management, the role of adjuvant chemotherapy, hormonal manipulation and radiotherapy remains of unproven value and cannot be recommended at this time.[4,5]

In this retrospective study, we have reviewed our experience with this peculiar tumor in an attempt to study its various clinical aspects and the results of different treatment modalities utilized in managing those patients.

Patients and Methods

During the period from 1980 to 1990, the Tumor Registry of King Faisal Specialist Hospital and Research Centre (KFSH&RC) identified 12 females with the diagnosis of cystosarcoma phyllodes who were referred to our institute for further management. The records of those patients were reviewed to obtain demographic data, clinical presentation, pathological characteristics, extent of disease and the outcome of different treatment modalities.

Results

Cystosarcoma phyllodes represented 0.8% of all breast cancers referred to our institute during the period of the study. Eleven patients were referred after 1985. Most of the referrals were from the Central and Southern regions of the Kingdom of Saudi Arabia (six patients from each area). Patient characteristics are shown in the table. The median age was 44 years (range 16 to 65). Seven patients (58%) were premenopausal while five were postmenopausal. Five patients were multiparous while seven were nulliparous (six were single and one had primary infertility).

All patients presented with unilateral breast mass. The right breast was as equally affected as the left. The tumor size ranged from 7 cm to 20 cm (median 11 cm). Seven patients (58%) had tumor size of more than 10 cm in greatest dimension. The median duration of the symptomatic mass was 15 months (range two to 174).

From the Departments of Medical Oncology (Drs. Ezzat, El-Senoussi, Wierzbicki, Bazarbashi, Abdel-Warith), Surgery (Dr. Abdulkareem), and Biomedical Statistics and Scientific Computing (Khan), King Faisal Specialist Hospital and Research Centre, Riyadh.

Address reprint requests and correspondence to Dr. Ezzat: Head, Section of Medical Oncology (MBC-64), King Faisal Specialist Hospital and Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia.

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TABLE: *Patient characteristics.*

Characteristics		Number	%
Age:		12	Median 44 Range 16-65
Sex:		12 F	100
Menopause:	Premenopausal	7	58
	Postmenopausal	5	42
Parity:	Multiparity	7	58
	Nulliparity	5	42
Duration of symptoms:			Median 15 mo. Range 2-17 mo.
Symptoms & signs:			
	Breast mass	12	100
	Skin ulceration	-	0
	Axillary lymph nodes	-	0

Clinically, none of the patients had palpable axillary lymph node enlargement at presentation. Initial metastatic work-up, which included chest film, liver ultrasonography (± computed tomography [CT] liver) and bone scan, did not reveal metastatic disease.

Surgery was the mainstay of the primary therapy. Nine patients (75%) underwent mastectomy (five simple mastectomies at the referring hospitals and four modified radical mastectomies at KFSH&RC). Three patients underwent wide local excision.

Review of pathology reports revealed all tumors to be malignant based on the degree of mitosis, stromal overgrowth/cellularity and necrosis. In the four patients who underwent modified radical mastectomy at KFSH&RC, none had axillary lymph node metastasis, while only one tumor was positive for both estrogen and progesterone receptors.

Two patients received postoperative locoregional irradiation (5300 cGy and 5600 cGy respectively) and adjuvant chemotherapy utilizing adriamycin 50 mg/m^2 and dacarbazine (DTIC) 375 mg/m^2 intravenously every three weeks for six courses.

Four patients relapsed at six, 11, 19 and 36 months respectively. Of these, one patient developed local recurrence and contralateral cystosarcoma phyllodes. She was the only patient in this series who developed bilateral disease. Another patient developed local recurrence and distant relapse to lung and liver metastases. It is noteworthy to mention that two local relapses were treated primarily by wide local excision. The other two relapses were to distant sites only (lung and bone).

One patient was lost to follow-up with no evidence of disease after two months following primary surgery. After median follow-up of 17 months (range two to 77), 10 patients were alive, nine with no evidence of disease. The projected five year survival by the Kaplan-Myer method is 83% for the whole group (Figure).

Discussion

Although cystosarcoma phyllodes is a rare tumor with incidence ranging from 0.3% to 0.9% of all breast cancers, it remains a challenge to clinicians and pathologists.[2] Since early in this century, it has been recognized that the natural history and clinical behavior of this tumor are different from carcinoma of the breast. The mean age in larger series is in the fourth decade;[6,7] however, there are cases reported in the prepuberty and adolescent period.[8,9] The median age in our series is 45 years, while our youngest patient was 16 years old. One of the salient features of cystosarcoma phyllodes is the very rare occurrence in men due to lack of a lobular-alveolar unit in the male breast.[10]

McDivitt et al. reported 40% and 70% incidence of multiparity in benign and malignant cystosarcoma phyllodes respectively.[11] In our series, 58% were multiparous. The significance of this observation is not known. Bilaterality is rare in either benign or malignant phyllodes tumor.[12,13] Only one patient in our series has bilateral disease. Most of our patients were referred from the central area (which has the highest population density and is the site of our center) and from the southern area for unclear reasons.

The most common presenting symptom is painless breast mass.[14] Pain and ulceration are not considered as signs of malignancy.[2] All our patients presented with breast mass without ulceration. Axillary lymph node metastasis is exceedingly rare despite a large mass, a situation infrequent with adenocarcinoma. On the other hand, axillary lymph node enlargement does occur (20% in the Norris and Taylor series);[12] this is virtually never due to metastasis but is rather due to infected, necrotic, ulcerated tumor causing enlarged hyperplastic lymph nodes. In four of our patients, axillary lymph node dissection did not reveal malignant involvement.

Criteria to classify benign, borderline and malignant cystosarcoma phyllodes have always utilized several histologic parameters such as cellular atypia, mitotic activity and tumor margin.[6,7,12,15-18] The complex

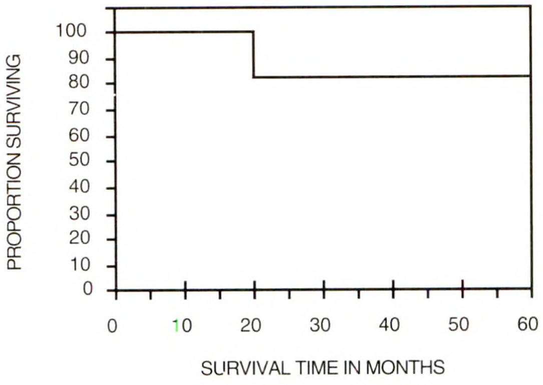

FIGURE: Projected five-year survival.

relationship between these variables has led to the formation of several grading systems, none of which could consistently predict the clinical behavior of these tumors. In recent studies from Northwest University (Chicago, Il, USA), the use of flow cytometric analysis of DNA aneuploidy and proliferative index correlated with the grading systems.[19,20] Although the reported incidence of malignant tumor is approximately 25% of all phyllodes tumors,[2] all our patients had malignant tumors in keeping with referral patterns to specialized institutes.[6,12,14]

Variable observations about the presence of estrogen and progesterone receptor in these tumors may reflect, in part, the relative amount of epithelium and stroma in individual phyllode tumors.[21-23] In our present series, only one of four tumors assayed proved to be receptor-rich.

Surgery remains the mainstay of primary treatment. Although most series recommended total mastectomy for large tumors, it is reasonable to perform wide local excision with a good safety margin (1 cm to 2 cm) for small tumors.[24] Some investigators recommend axillary lymph node sampling only if suspicious lymph nodes were detected clinically. In our series, nine patients underwent mastectomy. Of the three patients who were treated primarily by wide excision, one had local relapse and was rendered disease-free by another wide excision, while another patient had distant relapse as well as local recurrence. One remains disease-free. The use of chemotherapy, hormonal manipulation or radiation therapy as adjuvant therapy or for metastatic disease has been disappointing.[4,5] The lack of standard policies in managing these tumors has led two of our patients with tumor size >15 cm to receive adjuvant chemotherapy and radiation therapy at the discretion of their physician.

None of our patients presented with metastatic disease, but on follow-up, four patients (35%) had disease relapse. One patient had local relapse only, another had local and distant relapse while two patients had only distant relapses. In the literature, the incidence of distant relapse ranged from 3% to 12%[2] while local relapse was reported in 8%.[25]

The median survival time in our series is 30 months and the projected five year survival is 83% (Figure), comparable with 79% in a study conducted in Sweden.[26]

In conclusion, malignant cystosarcoma phyllodes has a different natural history from carcinoma of the breast. Review of the literature supports the use of wide local excision with a good safety margin for small tumors; otherwise, mastectomy is the preferred local treatment. The use of adjuvant chemotherapy or postoperative radiation cannot be recommended. The survival data from our series is parallel to reported series.

Acknowledgment

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VERY EARLY MORNING INCREASE IN ONSET OF ISCHEMIC STROKE

Sükrü Torun, MD; Gazi Özdemir, MD

A study was conducted on 525 consecutive patients ranging in age from 36 years to 86 years to determine whether diurnal variation occurs in the onset of acute ischemic stroke. There was a clear (D_{max}=0.19, $P<0.01$) diurnal variation with a significant (t=-4.96, $P<0.001$) peak between four a.m. and six a.m. Strokes occurred more often during the two hours following awakening than during any other time of the day. The peak time of ischemic stroke in our study was about two hours earlier than in previous reports, probably because of the different waking times of the studied populations. We concluded that the time of awakening influences the circadian distribution rather than the time of day itself. *Ann Saudi Med 1994;14(3):201-203.*

Ischemic vascular events have been reported repeatedly to occur following a circadian rhythm.[1-3] Most of these reports deal with myocardial ischemia,[4,5] acute myocardial infarction,[6,7] and sudden cardiac death.[8,9] Similar circadian variation of cerebral ischemia was also reported but with contradictory findings.[10-16]

While there are considerable variations in patient populations and methods, most of the previous studies note a peak onset in the morning hours,[17-19] particularly at the time of awakening.[20]

The aim of the present study was to investigate the possibility that acute ischemic stroke (IS) has a circadian variation and IS occurs more often at certain times of the day in Turkish sufferers whose awakening time is probably different from western populations.

Material and Methods

Prospectively collected data on 525 patients with acute IS, admitted to our Department of Neurology between December 1986 and May 1990 were analyzed. Only the cases in which the diagnosis of IS was ascertained by computed tomography (CT), and only strokes of acute onset in which symptoms reached their maximum in less than eight hours and remained present for more than three weeks were considered.

The time of onset of symptoms attributed to IS and the time of awakening were obtained from the patient, family members, or other observers.

We considered the time of onset to be the hour in which the patient or an observer first became aware of the event. In patients who first noticed their stroke symptoms on waking, it was presumed that the IS had occurred during sleep. Details of whether the patient was active or at rest when the IS occurred were also recorded.

The frequency of symptom onset was tabulated for two hourly intervals in the day beginning one minute after the previous hour (i.e., 12:01 a.m. to 2 a.m., 2:01 a.m. to 4 a.m., etc.). The Student's t-test and Kolmogorov-Smirnov type statistics were used for statistical analysis involving comparison of distributions of IS over a 24 hour period.

Results

Our study included 525 patients with acute IS, consisting of 295 males and 230 females ranging in age from 36 to 86 years (mean age 64.2). There was a clear and significant diurnal variation in IS occurrence (D_{max}=0.19, $P<0.01$). The proportion of IS occurring while awake was higher than while asleep (80% versus 20%). Whether onset of IS had occurred while awake or asleep, the variation was still significant (D_{max}=0.36, $P<0.001$ and D_{max}=0.30, $P<0.001$) (Table).

TABLE: *Time of onset of stroke during sleep or while awake.*

Time	Asleep**	Awake***	Total****
12 a.m. - 2 a.m.	9	12	21
2 a.m. - 4 a.m.	17	15	32
4 a.m. - 6 a.m.*	19	187	206
6 a.m. - 8 a.m.	24	16	40
8 a.m. - 10 a.m.	13	16	29
10 a.m. - 12 p.m.	2	89	91
12 p.m. - 2 p.m.	-	2	2
2 p.m. - 4 p.m.	-	6	6
4 p.m. - 6 p.m.	-	8	8
6 p.m. - 8 p.m.	12	63	75
8 p.m. - 10 p.m.	3	4	7
10 p.m. - 12 a.m.	6	2	8
Total	105	420	525

*=t = -4.96, $P<0.001$; **=D_{max} = 0.36, $P<0.001$; ***=D_{max} = 0.30, $P<0.001$; ****=D_{max} = 0.19, $P<0.01$.

From the Department of Neurology, Anadolu University School of Medicine, Eskisehir.

Address reprint requests and correspondence to Dr. Özdemir: Iki Eylül Cad. Yediler Sok. 1/11, 26010 Eskisehir, Turkey.

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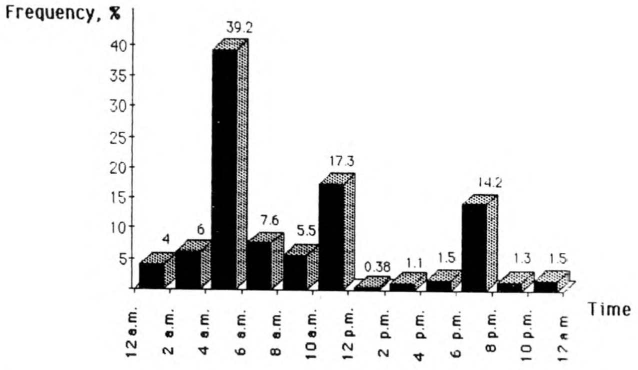

FIGURE: Frequency in two-hour intervals of the onset of ischemic stroke.

The maximum incidence of IS occurred between 4 a.m. and 6 a.m. (t=-4.96, $P<0.001$). A second similar peak was observed between 10 a.m. and 12 p.m. and there also seemed to be a third smaller peak between 6 p.m. and 8 p.m (Figure).

The interval between the waking time and the time of onset of IS was available in all of our patients, and 245 (53.8%) of 420 awake onset strokes occurred within the first two hours after waking. Stroke onsets occurring while having been awake for more than two hours showed a rather even distribution.

Discussion

It is widely accepted that onset of IS is not random during 24 hours but has a characteristic distribution. We also found clear evidence of diurnal variation in onset of IS in this study.

Regarding circadian time, our results are similar to those of other studies that have provided strong evidence suggesting that IS occurs most commonly in the morning.[10-18] Although several previous reports of diurnal variation in stroke suggested that stroke was more common at night during sleep,[1,19] no reasonable explanation is provided for the pathophysiologic mechanism leading to cerebral infarction. The possibility that stroke occurs during sleep but is noticed when the patient wakes up in the morning was ruled out in previous studies.[10,12,16] Our results support this conclusion, since a significant proportion of strokes occurred after awakening. The first hour after awakening seems to be the most common period of onset of IS, as had been reported.[12,16,20]

There are many factors that may contribute to circadian periodicity of the onset of IS. Blood pressure decreases during sleep and this occurs even when a nap is taken during the day.[21] However, because the evidence does not suggest an excess of IS during sleep, hypotension cannot account for most of our cases. Similarly, blood pressure decreases during sitting or resting and increases during physical activity.[22] The rapid physiologic increase in blood pressure, particularly after awakening in early morning, may lead to overresponse of autoregulation and may provoke a fragmentation of a carotid plaque, if present. In fact, the major peak of IS onset observed in our study occurred during that period. Nevertheless, this suggestion contradicts other studies that show no difference in the pattern of stroke between normotensive and treated or untreated hypertensive patients for all types of strokes.[9,11]

The relevance of other triggering factors remains unproven. Increase in platelet aggregatability and activation, [23,24] increase in hematocrit and blood viscosity,[25] increase in catecholamines and sympathetic tone,[24,26] decrease in fibrinolytic activity,[27] decrease in endogenous tissue plasminogen activator activity corresponding to levels of plasminogen activator inhibitor,[27,28] and circadian fluctuations in central dopamine activity,[29,30] may result in an increased susceptibility of the brain to ischemia during the morning hours.

No single factor is likely to explain the peaks for IS onset observed through the day in our study. The high rate of IS onset within two hours after awakening, and an additional two peaks in the late morning (10 a.m. to 12 p.m.) and in the evening (6 p.m. to 8 p.m.) suggest that the physical and emotional activities that occur during the awake period may be important. Thus, the onset of IS may be the result of the simultaneous occurrence of the above mentioned triggering factors and various activities, each by itself of little consequence, but may cause a cerebral infarction when occurring together.

The greatest peak onset of IS was found to be between 4 a.m. and 6 a.m. in our study. This is about two hours earlier than in most of the previous reports.[9-15] Different awakening times may be an acceptable explanation for this discrepancy. In Moslem populations, elderly people wake up very early in the morning to perform the first of their daily ritual prayers. We suggested that physiologic changes linked to awakening could be involved in the mechanisms causing the excess of IS in very early morning hours in our patients. Haapaniemi et al. have also reported that during weekends and holidays the morning strokes occurred about two hours later than during working days, probably because of differing awakening times.[16] Since different times of onset may reflect pathophysiologically different mechanisms, analyses of diurnal rhythms concerned with hemodynamic variations, neuroendocrine responses, fibrinolytic and thrombotic activities and physical or mental stress seem most likely to provide further information about the pathogenesis of IS onset.

Further studies are required to clarify the interactions between endogenous rhythms, exogenous rhythms and disease in different populations who have different customs, and in well-defined subgroups of patients with certain risk factors for stroke. A complete understanding of the primary significance of circadian variation of IS onset should permit progress in the prevention of disease.

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OVERWHELMING RESPIRATORY FAILURE ASSOCIATED WITH *LEGIONELLA PNEUMOPHILA*

Nabil S. Dahmash, MD; Mohamed Osman Gad-El-Rab, MD; Mohamad S. Al-Hajjaj, FRCP(C)

Four patients were admitted to the medical intensive care unit at King Khalid University Hospital (KKUH) with overwhelming respiratory failure. Extensive investigations revealed serological evidence of Legionella infection. Three patients required intubation and mechanical ventilation. All patients received erythromycin; rifampin was added to two patients. Two patients survived and two patients died. We report, for the first time in Saudi Arabia, four cases of *Legionella pneumophila* with severe respiratory failure. *Ann Saudi Med 1994;14(3):204-208.*

Although legionnaires' disease can cause severe progressive pneumonia[1-3] acquired by airborne transmission,[4,5] acute respiratory failure and adult respiratory distress syndrome are uncommon.[6-10] Rapid diagnosis is mandatory to initiate treatment as early as possible.[11-15] Bacteriological culture or documentation of the agent in tissues requires special media and stain and does not offer rapid diagnosis. A direct fluorescent antibody staining test (DFA) has been described for rapid diagnosis; however, it is positive in only 50% of culture-proven cases.[2] Alternatively, in the absence of a DFA test, presumptive diagnosis can be made if the titer of an indirect fluorescent antibody (IFA) test is ≥1:256[13] in addition to compatible clinical presentation.

In this report, we present our experience with four patients with legionnaires' disease who presented with a severe form of respiratory failure and who were subsequently diagnosed as having *Legionella pneumophila.*

Material and Methods

Patients

The subjects were comprised of four patients admitted to the Medical Intensive Care Unit (MICU) at King Khalid University Hospital (KKUH) in Riyadh, Saudi Arabia between July and October of 1992. They were diagnosed as having acute respiratory failure (ARF) and were subsequently proven to have *Legionella pneumophila.* Only patients in respiratory failure requiring monitoring in the intensive care unit were included. Criteria for diagnosis of adult respiratory distress syndrome (ARDS) included the following: PO_2 <50 mm/Hg on 60% or more fractional inspired oxygen concentration (FIO_2), rapidly progressive lung infiltrate on chest roentgenogram (CXR) in the absence of heart failure or fluid overload.

Laboratory Investigations

Routine laboratory investigations were performed on all patients. These included hemogram, erythrocyte sedimentation rate (ESR), urinalysis and electrolytes (U&E), arterial blood gases (ABGs), CXR, as well as bacteriological and serological tests. Additional tests were performed when indicated.

Flexible fiberoptic bronchoscopy and bronchoalveolar lavage (BAL) were performed when appropriate. Sputum and BAL specimens were examined by Gram's stain and cultured on buffered charcoal yeast extract agar containing L-cysteine and ferric ion and ketoacids.

Serological Tests

Freshly drawn blood was obtained by venipuncture from all patients on admission. The serum was separated and stored at 2°C to 8°C for appropriate serological investigations. For Legionella serology, the Zeus Scientific Inc. Legionella screening indirect fluorescent antibody (IFA) test system was used to assay the level of Legionella antibodies in patients' sera. The test procedure was strictly followed as indicated in the product insert. The sera were first screened together with positive and negative controls. Positive sera, on screening, were further titrated to determine the endpoints. The results were recorded as titration endpoints, which is the highest dilution producing a 1+ apple-green fluorescence. A standing or single titer ≥256 provided presumptive evidence of infection.

Case 1:

AM is a 47-year-old male Saudi engineer with a history of ethanol abuse, cigarette smoking (3 to 4 packs/day for 30 years) and hypertension. One week prior to admission to KKUH, he was admitted to another hospital with a three-day-history of nonproductive cough, high fever, excessive

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From the Departments of Medicine and Immunology, College of Medicine and King Khalid University Hospital, Riyadh.

Address reprint requests and correspondence to Dr. Dahmash: Consultant Pulmonologist and Head of MICU, P.O. Box 54803, Riyadh 11524, Saudi Arabia.

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sweating, weakness, malaise and progressive dyspnea. The initial CXR showed an infiltrate involving the right upper lobe. The patient was started on ampicillin 1 g and erythromycin 1 g intravenously every six hours. When his condition continued to deteriorate, he was transferred to KKUH for further evaluation and management.

Physical examination in the MICU revealed an obese male who was dyspneic. His blood pressure was 150/80 mm/Hg, pulse rate 140/min and rectal temperature 40°C. Examination of the chest revealed bilateral crepitations. The remainder of the physical examination was unremarkable.

Complete blood count revealed white blood cells (WBC) of 9700/mm^3 with normal differential, hemoglobin concentration of 15 g/dL, and platelet count of 193,000/mm^3, ESR 90/1h, and sodium 128 mmol/L. The rest of his laboratory findings were unremarkable. ABGs obtained on 100% non-rebreathing mask revealed PaO_2 of 49 mm/Hg, carbon dioxide tension ($PaCO_2$) 29 mm/Hg, pH 7.50, bicarbonate (HCO_3) 23 mmol/L and oxygen saturation 89%. His CXR showed diffuse infiltrates (Figure). Echocardiogram revealed normal left ventricular function.

The patient was intubated and placed on mechanical ventilation that was supplemented by positive end-expiratory pressure (PEEP). He was given erythromycin 1 g intravenously every six hours. Gram's stain of the BAL specimen showed abundant pus cells but no organism. Sputum and blood cultures were negative. The patient continued to have fever up to 40°C and his oxygenation deteriorated further. Methylprednisolone 1 g intravenously was administered on the second day. This was followed by improvement in the patient's oxygenation and decrease in FIO_2 requirement. However, the patient continued to have a high fever. On the third day of admission, the result of Legionella serology was obtained (IFA titer 1:256). Rifampin 600 mg was also added to the regimen and 24 hours later the patient became afebrile. He was subsequently weaned off mechanical ventilation and was extubated on the seventh day. The patient was discharged from the hospital in good condition after 18 days. His CXR cleared completely except for residual fibrotic changes in the right upper lobe. A repeat IFA titer four weeks later was 1:512.

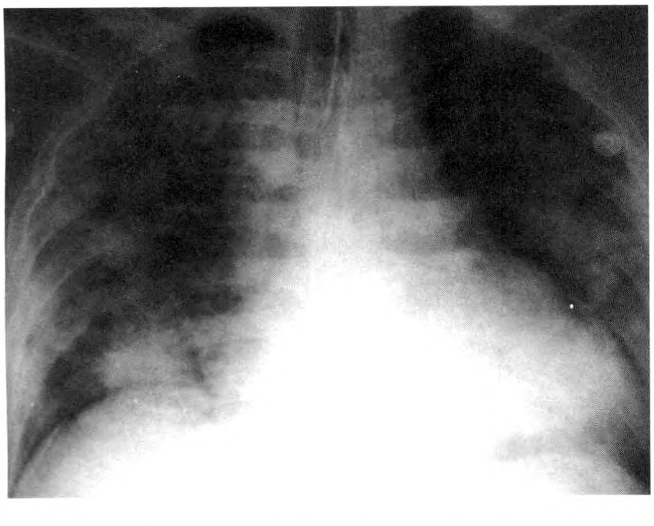

FIGURE: (Case 1) Chest roentgenogram showing widespread involvement of both lungs by alveolar infiltrate.

Case 2:

AF is a 69-year-old Saudi male, nonsmoker, with a history of lymphoma several years ago treated with immunosuppressive therapy. He was admitted to KKUH surgical intensive care unit following massive cerebral bleeding that was subsequently drained and he was placed on intravenous corticosteroids for increased intracranial pressure. On the 14th day of his hospital stay, the patient developed a right lower lobe infiltrate and high fever. Sputum culture revealed *Pseudomonas aeruginosa*. He was treated with appropriate antibiotics guided by antimicrobial sensitivity. However, the patient's condition continued to deteriorate and he developed extensive bilateral lung infitrates. His echocardiogram was unremarkable. He was transferred to the MICU on the 21st day.

On examination, the patient was unconscious, his blood pressure was 130/80 mm/Hg, pulse rate 110/min on controlled mode of ventilation and his temperature was 38.5°C. His WBC was 11,000/mm^3 with normal differential count, platelet count of 108,000/mm^3. His total bilirubin was 88 µm/L, direct bilirubin 48 µmol/L, serum aspartate aminotransferase (SGOT) was 102 U/L, serum aspartate alanine aminotransferase (SGPT) was 32 U/L, alkaline phosphatase 146 U/L.

ABGs obtained on 40% FIO_2 and PEEP of 5 cm H_2O were as follows: PaO_2 45 mm/Hg, $PaCO_2$ 37 mm/Hg, pH 7.46, HCO_3 24 mmol/L and oxygen saturation 83%. Legionella titer was requested. In spite of aggressive antibiotic therapy, the patient continued to have a high fever. Legionella titer available on the 27th day was 1:1024. He was started on erythromycin 1 g intravenously every six hours and rifampin 600 mg daily. His temperature subsided 24 hours later. A repeat IFA titer on the 40th day was 1:2048. However, the patient developed fulminant disseminated intravascular coagulopathy (DIC) and persistent hypotension. He died on the 42nd day. Blood culture obtained on the day of his death grew *Candida albicans*.

Case 3:

SM is a 50-year-old Saudi male with a history of diabetes mellitus. He has been a heavy smoker (more than three packs of cigarettes/day) for 25 years. He was admitted to another hospital with a four-day-history of nonproductive cough, fever and progressive dyspnea. The patient was started on erythromycin 1 g intravenously every six hours. However, his condition continued to deteriorate and the next day he was transferred to KKUH.

On examination, the patient was dyspneic and cyanotic. His blood pressure was 120/80 mm/Hg, pulse rate 120/min, respiratory rate 35/min, and rectal temperature 38.5°C. Examination of the chest revealed bilateral crepitations.

Complete blood count showed WBC of 17,000/mm^3 with a normal differential. His urinalysis and electrolytes and liver function tests were normal. CXR revealed extensive bilateral infiltrates with a small bilateral pleural effusion that was confirmed by ultrasound examination. Echocardiogram showed normal left ventricular function. ABGs obtained on 60% Venturi mask showed PaO_2 of 67 mm/Hg, $PaCO_2$ 41 mm/Hg, pH 7.39, HCO_3 28 mmol/L and oxygen saturation 96%. On the third day, the patient's condition deteriorated further. He was intubated and placed on mechanical ventilation supplemented by PEEP. His arterial blood gases on 100% FIO_2 were as follows: PaO_2 49, $PaCO_2$ 35, pH 7.44, HCO_3 23 mmol/L, and oxygen saturation 87%. BAL Gram's stain revealed pus cells but no organisms. When his oxygenation deteriorated further, intravenous methylprednisolone was given. This was followed by improvement in oxygenation. On the fourth day, Legionella titer was available (1:256). Rifampin 600 mg p.o. daily was added. However, the patient continued to have fever up to 40°C. Quantitation of immunoglobulin revealed an IgG of 3 g/L (normal 7.0 to 13.5 g/L). Intravenous immunoglobulin was administered. Multiple blood and sputum cultures revealed no growth. The patient developed profound hypotension and expired on the 14th hospital day.

Case 4:

NG is an 18-year-old Saudi soldier, previously healthy. He smoked one pack of cigarettes/day for three years. Two weeks prior to admission, he developed an upper respiratory tract infection followed by fever and cough, excessive sweating and progressive dyspnea. One day prior to admission the patient developed hemoptysis, left-sided pleuritic chest pain and dizziness.

On examination, the patient was drowsy and tachypneic. Blood pressure was 140/70 mm/Hg, pulse rate 92/min, respiratory rate 28/min, and temperature 40°C. Chest auscultation revealed bilateral crepitations in the lower lung zones. His WBC was 14,000/mm^3 with normal differential. The remainder of the laboratory tests were unremarkable. Arterial blood gases obtained on 40% FIO_2 revealed PaO_2 56 mm/Hg, $PaCO_2$ 33 mm/Hg, pH 7.37, HCO_3 23 mmol/L, and oxygen saturation 96%. His CXR disclosed infiltrates in the lingula, left lower and right middle lobes.

The patient was started on erythromycin 1 g every six hours and oxygen via Venturi mask. He became afebrile within 24 hours and his general condition improved gradually. Blood and sputum cultures were negative. Legionella titer available on the third day was 1:256. The infiltrate on his chest x-ray resolved completely within 10 days. He was discharged from the hospital in good condition on the 12th day.

Discussion

Diagnosis of *Legionella pneumophila* was made by compatible clinical history and the absence of any other etiologic agent known to cause pneumonia. The diagnosis was confirmed by elevated *Legionella* IFA titer and the response to specific treatment. The incidence of Legionnaire's disease ranges from 1% to 15% and around 1% to 40% of nosocomial pneumonitis.[16] The pneumonia occurs either in discrete outbreak or as sporadic cases.[9,10] *Legionella* species can survive for a long period of time in water and has been found in moist soil. This may explain the association of infection with recent excavation, air conditioner cooling towers, respiratory devices and humidifiers.[3,5,11] Three of our patients (Cases 1, 3 and 4) had community-acquired legionellosis, and one patient (Case 2) acquired the infection while in the hospital. The source of infection in all our patients was not identified. Although ARF and ARDS have been reported with Legionella infection,[2,10] to our knowledge no cases have been reported from Saudi Arabia. In a study of 567 episodes of pneumonia from the Al-Qassim region in Saudi Arabia, none of the patients were diagnosed as having *Legionella pneumophila*.[8] However, the study was retrospective and had its limitations. Legionnaires' disease is probably underdiagnosed and underreported in the Saudi population.

Legionella pneumophila affects patients of all age groups. However, adults are more likely to be affected than children. Men are affected two to three times more than women.[2,3] All patients in this report were males. Risk factors for acquisition of the infection include heavy smoking, alcohol abuse and diabetes mellitus. Prior surgery was found to be a major predisposing factor for nosocomial legionellosis in some studies.[1,3] Legionnaires' disease in immunocompromised patients, including renal transplant, may be more severe and more frequently lethal than in the general population.[12] Three of our patients were smokers (Cases 1, 3 and 4), one patient had a history of ethanol abuse (Case 1), one patient with diabetes mellitus and selective IgG deficiency (Case 3), and another (Case 2) had a history of lymphoma several years before admission; in addition, he was on a high dose of corticosteroids.

Typically, patients with *Legionella pneumophila* present with abrupt onset of malaise, myalgia, headache and progressive dyspnea. Cough is nonproductive early in the illness and minor hemoptysis may be present.[2,3,11] Chest pain, often pleuritic in nature, may be present.[11] Disorientation, obtundation and gastrointestinal symptoms may predominate the clinical picture.[2,11] Fever, nonproductive cough and progressive dyspnea were present in all patients except one (Case 2), who was unconscious and on mechanical ventilation. Hemoptysis was seen in one patient (Case 4). Laboratory findings in *Legionella pneumophila* are usually nonspecific with the exception of hyponatremia.[12,13] This was seen in only one of our patients (Case 1).

Initial CXR findings are nonspecific but commonly reveal a patchy interstitial or alveolar infiltrate involving one lobe of the lung.[14,15] Rapid progression of the infiltrate is common. Pleural effusion has been reported in 20% to 60% of cases.[16] Improvement is usually apparent on chest x-ray in one to two weeks after therapy. However, complete resolution of the infiltrate may require a longer period of time.[12] Two of our patients (Cases 1 and 2) initially had lobar consolidation, and two patients (Cases 3 and 4) had patchy infiltrate. Rapid resolution of the infiltrate occurred in two patients (Cases 1 and 4). However, in one patient (Case 1), minimal residual infiltrates were seen on CXR taken seven weeks following the acute episode.

Laboratory diagnosis may be very difficult. Positive DFA may be an objective marker for advanced disease;[2,17] however, this test is not available in our hospital. Culture of the organism is difficult and not available in the majority of hospitals in Saudi Arabia. Culture was attempted in three of our patients (Cases 1, 3 and 4); all were negative. This could have been due to prior administration of antibiotics, inadequate or poor quality of sputum or BAL samples, in addition to fastidiousness of the organisms to grow. Alternatively, the IFA test is positive in over 80% of patients with Legionnaires' disease.[16] In the Saudi population, Higham et al.[18] performed IFA tests on 224 patients from outpatient clinics and tested sera from 200 blood donors. In their study, 72% of the sera had an antibody titer of <1:16; 20% had titers between 1:16 to 1:32, and 8% had titers ≥1:64. The latter was thought to be significant and should be correlated with the clinical presentation of the patients. The repeat titer was performed for two patients only (Cases 1 and 2), but was not done for the remaining two patients since one patient (Case 4) did not come back for follow-up visit and the other patient expired.

Mechanical ventilation supplemented by PEEP may be necessary when hypoxemia is severe. Two of our patients with ARDS (Cases 1 and 3) required mechanical ventilatory support. Another patient (Case 2) was already on mechanical ventilation when he developed *Legionella pneumophila*. Intravenous erythromycin is the drug of choice and should be instituted as early as possible in highly suspected or confirmed cases.[2,12] In our study, all patients were suspected of having *Legionella pneumophila* based on clinical features; therefore, treatment with erythromycin was initiated in three patients before the results of the IFA titer were available. Response to therapy is usually dramatic and occurs within 24 to 48 hours, as seen in two of our patients (Cases 2 and 4), although fever may persist for a longer period (Cases 1 and 3).[12] Rifampin may provide an effective addition to erythromycin in selected Legionnaires' disease patients. Kovick et al.[1] recommended the routine usage of a combination of erythromycin and rifampin as initial therapy for confirmed Legionnaires' disease when associated with positive DFA, bilateral or multilobar infiltrate, use of glucocorticoid therapy, or in case of failure to respond following 72 hours of erythromycin therapy. Two of our patients (Cases 1 and 3) received rifampin in addition to erythromycin. Corticosteroids, to our knowledge, have not been used in *Legionella pneumophila* previously. The use of this drug in ARDS is controversial.[19] Corticosteroids were given in two of our patients (Cases 1 and 3) because of progressive deterioration of their condition. However, we do not recommend the routine use of this drug in Legionnaires' disease.

In conclusion, pneumonia caused by *Legionella* species is a serious disease that may lead to ARF and ARDS. It should be treated aggressively with a combination of erythromycin and rifampin in selected cases. Both physician awareness and availability of specialized laboratory tests are necessary for establishing a diagnosis.

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FACTORS AFFECTING THE USE AND ATTITUDE TOWARDS MEDICAL RESOURCES AND EDUCATIONAL METHODS IN A SAUDI MEDICAL SCHOOL

Waleed A. Milaat, MD, PhD(UK); Fathi M. El-Gamal, MD. PhD(UK)

Medical colleges are using various teaching methods and educational resources in education. In order to explore the attitude of medical students towards these educational methods and resources and the factors playing a major role in their use in a medical school in an Arabic culture, a self answered questionnaire was directed to 283 medical students in their clinical years. Questions on the possible factors which affect the attendance and the use of these education resources were also included. Traditional methods of teaching, lectures, and clinical rounds were found to be the backbone of the educational process in this college. Attendance to lectures was related to both quality of subjects and to the lecturer, emphasizing the importance of a good lecture and lecturer. Clinical bedside teaching was found to be a popular and effective way of teaching medical knowledge, skill, and patient interactions to medical students. The library in this college was the least used resource and student appreciation of its importance was very low. General recommendations are to reduce dependence on lectures gradually in clinical years and to introduce new methods of clinical teaching. *Ann Saudi Med 1994;14(3):209-214.*

The education process in medical colleges is aiming, in its broad term, to produce a competent general practitioner oriented to the health problems of the community.[1] In fulfilling this, colleges are using various teaching methods and educational resources. Although some medical colleges are using advanced methods such as computer-aided discussion of clinical cases, student discussion groups, integrated sessions and open seminars, traditional methods of teaching, namely lectures and clinical rounds, are still considered the backbone of this educational process and, clearly, the most feasible ones.[2] The medical library, on the other hand, is the most commonly available educational resource in most medical schools. It is the intention of this paper to explore the attitude of medical students toward these educational methods and resources and the factors playing a major role in their use in a medical school in an Arabic culture and to present some recommendations for their effective use.

The College and the Educational Process

The medical college in King Abdulaziz University in Jeddah, Saudi Arabia operates an undergraduate program for six years following secondary school. The first three years are for basic medical science teaching while the other three years are dedicated to clinical teaching. Teaching in the clinical years is performed in the form of bedside teachings (clinical sessions or rounds) and formal 50 minute lectures.

The quantity of lectures and clinical rounds varies in various years but generally, lectures encompass 35% to 40% of the curriculum with clinical sessions making up the remaining 60% to 65%. Slide presentations and overhead transparencies are commonly used in lectures. Student presentation of clinical cases is the usual method of clinical sessions that are followed by comments, short group discussion and explanation by the accompanying tutor. Students who do not attend 20% of their lectures or clinical sessions are penalized by deducting part of the marks allocated for their interval exams or preventing them from sitting for final exams. The medical library of this college in the male campus opens 10 to 12 hours daily. It contains various assigned textbooks, study corners, audiovisual aids, a wide range of medical journals and some reference books in clinical medicine and basic medical sciences. Another smaller library is located in the female section. In this Islamic country, the college is actually a two-in-one college, as segregation of the sexes is a fundamental pillar of the training.[3] Hence, two separate libraries are available for females and males while lectures and clinical rounds are repeated for each sex by the same or a different tutor.

Subjects and Methods

The present study was conducted by administering a detailed questionnaire to medical students in the fourth, fifth, and sixth years (N=367 students), inquiring about personal characteristics, hobbies and social activities, his/her grade for the previous academic year and his/her use

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From the Department of Community Medicine and Primary Health Care, Medical School, King Abdulaziz University, Jeddah.

Address reprint requests and correspondence to Dr. Milaat: P. O. Box 984, Jeddah 21421, Saudi Arabia.

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and attitude towards educational methods and resources; namely, lectures, clinical sessions, and library. Questions on the possible risk factors that might affect the attendance and the use of these educational resources were put to students with extra space for personal opinion. In order to obtain students' opinions freely, they were requested not to write their names. Personality traits of the students were studied using Eysenck Personality Test,[4] where two scales were considered (namely neuroticism scale and introversion/extroversion scale). A total of 284 students from the whole group returned the questionnaire.

Statistical Analysis

Data were analyzed using IBM PC and Statgraphics Version 4 statistical package.[5] Data were subjected to simple statistical methods as well as to principal component regression technique,[6,7] where the following steps were performed:[8,9] 1) the original data were standardized (centered and scaled); 2) a cross-correlation matrix between the variables was prepared; 3) factors were extracted using the principal component solution without iteration. In this method, the main diagonal of the correlation matrix is not altered and the program extracted principal components that are defined as exact mathematical transformation of the original variables. A variable can be decomposed into components and predicted exactly from these components; 4) the extracted components were rotated using "Varimax" type of rotation to obtain orthogonal factors with simple structures; and 5) regression of the dependent variable was performed on the rotated components using stepwise regression technique. The variable was considered significant if the P value was <0.05.

Results

The sample comprised 77.4% of total students in three clinical years; 39% in the fourth year, 31% in the fifth year, and 30% in the sixth year. The male to female ratio of our study population was 1.4:1 and the ratio of single to married students was 1:2.7. The majority of students were nonsmokers (85.9%). The age distribution was as follows: 22 to 23 years (32.4%); 24 to 25 years (62.0%); and 26 years or more (5.6%).

Figure 1 shows the use of various educational methods and resources in both sexes. Answers to questions regarding the student's attitude and use of various

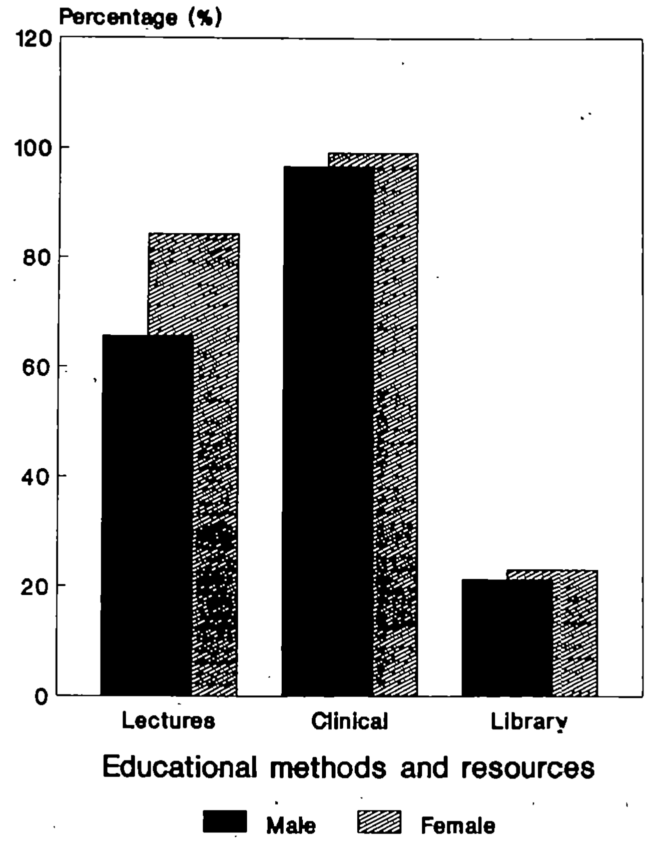

FIGURE 1. Use of methods and resources by medical students according to sex.

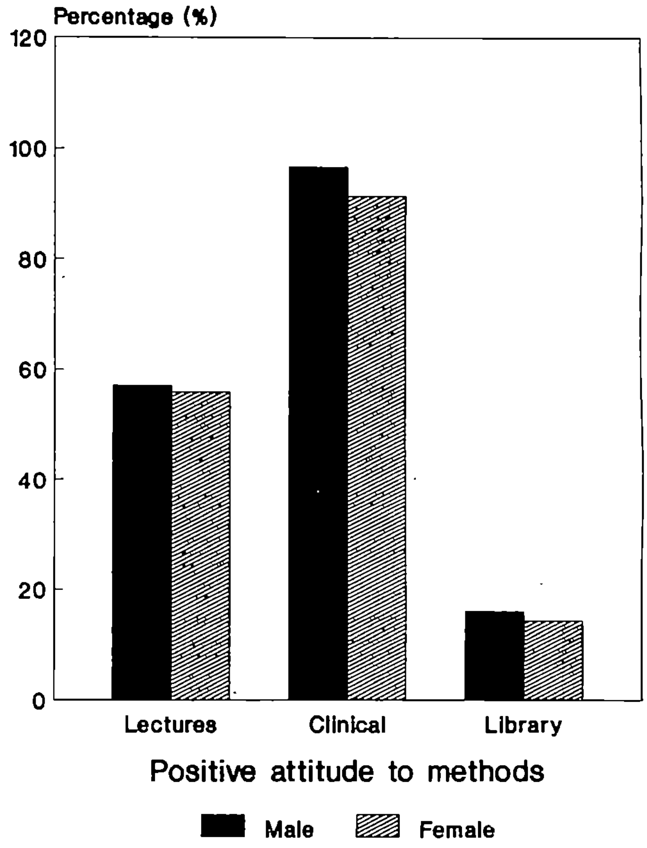

FIGURE 2. Attitude of medical students towards educational methods and resources according to sex.

educational resources and methods, and factors that attract or deter them are included in Table 1. The majority (94.5%) of the students considered clinical rounds an important factor for success and 56.6% felt the same regarding attendance to lectures, while only a minority (16.6%) had the same attitude toward the use of the library (Figure 2). The actual use of these educational methods and resources by students showed similar trends (89.4%, 74.1%, and 20.7% respectively).

The main reasons that attracted students to attend lectures were the scientific material presented (91.5%) and personality of the lecturer (73.4%), while only 28.8% of the students considered marks allocated to the subject as an important factor for attending lectures. The main factors that deterred students from attending clinical rounds regularly were personality of the tutor, the feeling that the subject of the session was useless, and the far location of the training hospitals from the faculty of medicine.

A total of 225 students (79.3%) in both sexes did not use the library and 187 of them (66%) felt that the main reason for this was the lack of time in their busy schedule. Several social and personal factors of the students were significantly associated with their attendance to lectures (Table 2). Females regularly attended lectures compared to males ($P<0.005$). Living in campus accommodations was associated with less attendance to lectures ($P<0.05$). A positive relationship was found between the presence of the father at home and attendance to the lectures ($P<0.005$). Students who smoked or joined private clubs were less likely to attend lectures ($P<0.005$), as well as students who were allowed to be away from home or to come late to the home ($P<0.01$).

Educational variables associated with attendance to lectures are cited in Table 3. There was a negative relationship between high rank of academic year and attendance to lectures, as sixth year students attended less than fifth and fourth year students ($P<0.05$). Students with high grades in the previous year (very good or excellent) were significantly better attendees to lectures ($P<0.05$). There was a positive association between attendance to clinical rounds and the frequent use of library with attendance to lectures ($P<0.001$; $P<0.05$ respectively). A highly positive relationship was found, as expected, between positive attitude toward lectures and attendance ($P<0.001$).

Table 4 depicts the relationships between rotated principal components and various variables. It is obvious that each factor (after rotation) is identified mainly with one of the original variables; for example, the correlation coefficient (r) between factor one and the variable (academic year) is 0.94, i.e., 88.34% (which is r^2) of the variance in the variable (academic year) was explained by factor one, or the weight of factor one was mainly determined by the academic year variable while other

TABLE 1. *Use and attitude of medical students towards educational methods and resources.*

Item	% Said Yes
Lectures	
Lectures are important for success	56.5
Attended most of the lectures (>90%)	74.1
Reasons for attendance:	
Scientific material presented	91.5
Personality of the lecturer	73.4
Time of the lecture is suitable	64.5
Recording of attendance	55.8
Employment of audiovisual aids	50.7
Unavailability of textbooks	40.8
High marks allocated to the subject	28.8
Clinical Rounds	
Clinical rounds are important for success	94.5
Attend all the clinical rounds	89.4
Reasons for not attending clinical rounds:	
Personality of the tutor not convincing	10.2
The session subject was not useful	07.0
Training hospitals are far from the University	06.0
No recording of attendance	03.0
Library	
Use of library is important for success	16.6
Used library regularly	20.7
Reasons for not using library:	
Lack of time	66.0
Library is too noisy	39.5
Unavailability of good textbooks	21.1

TABLE 2. *Relationship of lecture attendance to personal and social factors.*

	Attending lectures				
	Yes (n=210)		No (n=73)		
Factors	n	%	n	%	x^2
Sex					
Male	103	66.0	53	34.0	
Female	107	84.3	20	15.7	11.23***
Live on University Campus					
Yes	59	65.6	31	34.4	
No	151	78.2	42	21.8	4.52*
Presence of father at home					
Present all year	127	79.4	33	20.6	
Travels occasionally	57	77.7	17	23.0	
Travels most of the time	7	38.9	11	61.1	
Dead	18	64.3	10	35.7	15.86***
Smoking habits					
Non-smokers	192	78.7	52	23.3	
Smokers	18	46.2	21	53.8	18.59***
Joining Private Clubs					
Yes	25	58.1	18	41.9	
No	183	77.2	54	22.8	6.90***
Permission to be away from home					
Yes	83	66.9	41	33.1	
No	127	80.4	31	19.6	6.60**
Permitted to return home late					
Yes	101	67.8	48	32.2	
No	109	81.9	24	18.1	7.42**

*=$P<0.05$; **=$P<0.01$; ***=$P<0.001$.

TABLE 3. *Relationship of lecture attendance and educational factors.*

	Attending lectures				
	Yes (n=210)		No (n=73)		
Factors	n	%	n	%	X^2
Academic Year					
Fourth	89	80.9	21	19.1	
Fifth	66	75.9	21	24.1	
Sixth	55	63.9	31	36.1	7.43*
Previous Year Grade					
Failed	13	76.5	4	23.5	
Passed	60	65.9	31	34.1	
Good	93	73.2	34	26.8	
Very good	36	90.0	4	10.0	
Excellent	7	100	0	0.0	10.98*
Attended Clinical Rounds					
100%	187	72.2	62	27.8	
>75%	8	50.0	8	50.0	
50% - 75%	0	0.0	1	100	7.59*
Use of Library					
Yes	53	84.1	10	15.9	
No	157	71.4	63	28.6	4.14*
Feel that lectures are important for success					
Yes	126	82.9	26	17.1	
No	72	60.5	47	39.5	17.00***

*=$P<0.05$; **=$P<0.01$; ***=$P<0.001$.

TABLE 4. *Correlation between factors and various variables.*

Factor No.	Variables	r
1	Academic year	0.94137
2	Last year grade	0.95604
3	Having friends	0.96958
4	Smoking habits	0.97574
5	Permitted to study out	0.96300
6	Join university activities	0.95962
7	Marital status	0.97488
8	Family size	0.97063
9	Campus residence	0.98096
10	Permitted to be away from home	0.97368
11	Monthly expenditure	0.94560
12	Extrovert personality trait	0.96058
13	Permitted to return home late	0.92662
14	Sex	0.93396
15	Join private clubs	0.97063
16	Neuroticism personality trait	0.91734
17	Age of the student	0.90446

variables have very low correlation with factor one. In other words, factor one can be used to represent the variable academic year only. The remaining factors showed similar relationships with different variables and each factor mainly represented the corresponding variable.

When these factors were used in the regression analysis to explain the variation in the outcome variable namely nonattendance to lectures (Table 5), it was found that factors representing the academic year of the student, previous year grade, smoking habit, joining private clubs, allowed to be away from home, monthly expenditure, family size, and sex were significantly associated with attendance to lectures. Attendance to clinical sessions was similarly affected by the above mentioned variables in a similar regression analysis.

Discussion

The use of various methods of teaching is dictated mainly by the structure of the curriculum, teacher preference, and the available resources. The use of the lecture method is still a cornerstone of medical teaching but many researchers are studying the superiority of other methods of clinical teaching on traditional lectures. Moore and Schare et al.[10,11] noted that performance of students taught by lectures and by problem-based learning (PBL) was identical but students preferred PBL to lectures. Harvey and Vaughan[12] found that lectures were the least favored teaching activity among nurses when studying their attitude towards 10 methods of clinical teaching. Ferreira[13] recommended less use of traditional lectures in clinical years and the wide use of integrated sessions. In the traditional Saudi culture, it seems that lectures still have a major role in medical education and students cannot be weaned completely from them, as 56.5% of students have a positive attitude toward lectures and 74.1% of them were regular attendees. Direct reasons related to lecture attendance in this college were related to both the subjects presented and the method of presentation as well as to the personality of the lecturer. More than half of the students found the use of audiovisual aids in a lecture as a good reason for attending and 73.4% were influenced by the personality of the lecturer. Attendance to lectures was fairly highly related to absence-taking during lecture and only minimally to the magnitude of marks allocated to the subject. This supports the importance of good lectures and the lecturer as a vehicle to train medical students and this point was echoed by the World Conference of Medical

TABLE 5. *Regression equations describing the relationship between factors and their representing variable with nonattendance to lectures.*

Factor No.	ß	t-value	
1	-0.0604	-2.2707	*
2	0.0590	2.2267	*
3	-0.0111	-0.4201	
4	-0.0744	-2.8040	**
5	-0.0270	-1.0168	
6	-0.0040	-0.1576	
7	-0.0304	-1.1479	
8	-0.0635	-2.3909	**
9	0.0058	0.2192	
10	-0.0522	-1.9626	*
11	-0.0532	-2.0027	*
12	-0.0647	-2.4396	*
13	-0.0236	-0.8876	
14	-0.0366	-1.3796	
15	-0.0662	-2.4950	**
16	-0.0277	-1.0419	
17	-0.0345	-1.2980	

*=$P<0.05$; **=$P<0.01$; ***=$P<0.001$.

Education, which stressed that medical teachers must acquire a set of skills that encourages and facilitates learning, especially independent and self learning.[1] This surely applied to teaching in the clinical field where bedside teaching is used to deliver medical knowledge and train future doctors in skills of communication, clinical examination, and patient management. It was obvious that clinical teaching by bedside teaching in small group discussion was a popular and favored way of teaching medical knowledge, skill, and patient interactions to medical students in this college. This can be seen from the homogenous high attendance and the positive attitude to clinical rounds from all years in both sexes (Figures 1 and 2). This is in agreement with Levenkron et al.[14] findings in their comparative study of effective teaching by patient instruction and small discussions, which resemble the method used in this college. It is still too early and premature to apply the highly sophisticated type of clinical teaching in our college such as computer assisted learning, since there is still controversy regarding the value and application procedure as well as to the influence on achievement compared to the traditional small group discussion in bedside teaching.[15,16] These methods need a well-structured curriculum and a dedicated and well-trained faculty staff for their implementation.

When studying the effect of several variables on the attendance and use of various educational methods and resources, it was obvious that variables of wide diversity were showing influence and they should be grouped for easier interpretation. Multiple regression analysis has been widely used as a standard technique to study the partial effect of predictor independent variables on an outcome variable,[7,8] but when the correlation matrix of all independent variables was examined, it was found that most of these variables were highly correlated ($r > 0.4$). In fact, when regular regression analysis was performed, only three variables out of the 17 independent variables turned out to be significant in explaining the variance in the outcome variable; namely, nonattendance to lecture, although most of these 17 variables were significant at the simple bivariate analysis level (Tables 2 and 3). This is related to the effect of multicolinearity in these highly intercorrelated data.[8,9] Factor analysis solved this problem by abstracting the net effect of each variable in a factor. It showed reasons for not attending lectures or clinical rounds to lie within three different areas: 1) student personality represented by extroverted personality, sex, smoking habit, and staying outside for long periods of time. These factors seem to be in logical harmony, as those who were attending more were nonsmokers, less prone to be extroverted, females, and not allowed to stay out of the home for a long time in the Saudi culture; 2) the socioeconomic status of the student, showing students with high expenditure, large family size, and those joining private clubs to be less attendant to lectures. This relationship of attendance to socioeconomic status is difficult to interpret. It is surely related to the dominant socioeconomic level and the culture of the society studied. We can only assume that some students from rich families are less motivated to attend and students with large family size who might have more family involvement and less time for attendance; and 3) educational factors related to attendance were represented by previous year achievements and the academic year as expected. The association of late clinical years with less attendance supports the recommendation by Ferreira[13] to reduce dependence on lectures to a minimum gradually in clinical years. The use of the library was found to be very low in this college. Direct reasons for this were related to time pressure on medical students (66%), the noisy environment, and the book service. These factors might explain the low rate of library use to a large extent but not the negative feeling towards its importance for success. The latter finding is extremely alarming, as only 16.6% of our future doctors felt positive towards the library. This point will need to be studied more in depth, since it will definitely affect their free reading out of assigned textbooks and capability for future research and will have a negative influence on their continued medical education after graduation. The persistent influence of the traditional pattern of premedical education in secondary schools in Saudi Arabia that depends on student memorization of assigned books and less use of library or outer sources in readings can be thought of as one of the important factors worth further research. Another factor might be related to the curriculum structure of this college that does not encourage self learning or library assignments.

In conclusion, lectures have a major role in the teaching process in this college and attendance was related to both the quality of subjects and to the personality of the lecturer in addition to the use of audiovisual aids. This supports the importance of good lectures and dedicated lecturers in training medical students. Clinical bedside teaching was found to be a popular and effective way of teaching medical knowledge, skill, and patient interactions to medical students. Most of the students had a positive attitude and high attendance. Library use was low and students described a disturbingly low appreciation for its role. Further research is needed to investigate this alarming phenomenon. General recommendations are to reduce dependence on lectures gradually in clinical years and to introduce new methods of clinical teaching.

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DIAGNOSTIC AGREEMENT BETWEEN PRIMARY CARE PHYSICIANS AND NEUROLOGISTS

Lubna A. Al-Ansary, MSc, MRCGP; Saad M. Al-Rajeh, MD

The ability of primary care physicians (PCPs) to diagnose neurologic disorders was assessed from the records of 166 patients referred to the neurology outpatient clinic in one year. At the time of referral, 74.7% were correctly diagnosed. Primary care physicians were competent in the diagnosis of cerebrovascular accidents, epilepsy, space-occupying lesions, dementia, extrapyramidal and cerebellar disorders. More specific diagnosis was difficult at the primary care level in cases of headache, spinal cord and peripheral nerve disorders. The implications of these results and possible reasons for them are discussed. Solutions to improve on this situation are recommended with emphasis on both undergraduate and postgraduate training in neurological bedside skills. The complementary roles of the primary care physician and the neurologist are stressed. *Ann Saudi Med 1994;14(3):215-218.*

Disorders that affect the nervous system are frequently encountered in the practice of family medicine. It has been estimated that neurologic disorders affect about 9.5% of the entire United States (US) population.[1,2] Each year 2.5% of the population will require the attention of a physician competent in clinical neurology. Herpes zoster, migraine and other severe headaches, and brain trauma have the highest annual incidence rate.[2] In the United Kingdom (UK), the prevalence of nervous system disorders is on the order of 11.2% to 14.4% for both males and females, and has shown an increasing trend in the last 20 years, but still very much of the pattern and scale as in Canada and the US.[3,4] Migraine and other severe headaches, epilepsy, stroke and transient ischemic attacks, dementia, and Parkinson disease are the major neurologic disorders that are prevalent in the population.[2,5,6] The most common neurologic problems referred to specialists are those disorders that are most frequently encountered by general practitioners such as headache, epilepsy, and unexplained symptoms such as giddiness and light-headedness.[4,7]

Data on the incidence and prevalence of neurologic disorders in Saudi Arabia are scanty.[8] Analysis of consecutive cases seen in the neurology outpatient clinics in the Qassim Region and the Eastern Province showed that seizure disorders, headaches, peripheral neuropathies and stroke were the most commonly encountered disorders in all age groups.[9,10] In both series, inherited disorders were frequent and accounted for 5% to 7% of the cases.

Primary care physicians (PCPs) should have sufficient education, training, and experience to recognize and manage most of the common neurological disorders encountered in ambulatory care.[1,4] A definitive diagnosis is central to successful management.[11] This may seem obvious for life or death emergencies but is also vital in chronic illnesses such as epilepsy and Parkinson disease if incorrect treatment is to be avoided.[6,11,12] The need to arrive at a definitive diagnosis often forms the basis for referral. In other situations, however, where the diagnosis is clear-cut, referral is often sought for confirmation and for guidance in management.

This paper reports the results of the evaluation of the neurological correctness of diagnosis by PCPs in case referral from primary care clinic to the neurology outpatient clinic. It identifies certain diagnostic categories in which the PCP commonly seeks clarification of the underlying definitive diagnosis.

Method

The study was conducted at one primary care center (PCC) based at King Khalid University Hospital (KKUH), the main teaching hospital in Riyadh, Saudi Arabia. The PCC is staffed by 12 PCPs (six male and six female). None of them had worked in neurology after graduation. Patients have open access to this center and the PCPs may therefore see patients coming from outside Riyadh. They have complete freedom of referral. Referrals made by the residents, however, are usually counterchecked and countersigned by the consultants. Physicians in this center see only those over 12 years of age.

All records of patients referred to the neurology outpatient clinic from August 1990 to July 1991 were retrospectively reviewed by one of the authors (LAA).

From the Departments of Family and Community Medicine (Dr. Al-Ansary) and Neurology (Dr. Al-Rajeh), King Saud University, Riyadh.

Address reprint requests and correspondence to Dr. Al-Ansary: P.O. Box 4556, Riyadh 11412, Saudi Arabia.

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TABLE 1. *Percentage distribution of reason for referral according to the primary diagnosis.*

Primary diagnosis	Number of cases	Reason for referral (%) Evaluation/Investigation	Treatment/Management	Advice/Reassurance	No reason recorded
Epilepsy	51	37.3	29.4	3.9	29.4
Headache	30	53.3	30.1	3.3	13.3
Extrapyramidal & cerebellar disorders	23	47.8	26.1	0.0	26.1
Spinal cord disorders	15	53.3	26.7	0.0	20.0
Peripheral nerve disorders	14	28.6	35.7	7.1	28.6
Cerebrovascular accidents	12	33.3	0.0	16.7	50.0
Space-occupying lesions	6	50.0	33.3	0.0	16.7
Dementia	5	60.0	20.0	0.0	20.0
Others*	10	80.0	10.0	0.0	10.0
Total	166	45.8	25.9	3.6	24.7

*=psychosomatic complaints, vertigo, nonspecific numbness, spasm, post traumatic amnesia and stammering of speech.

The diagnosis at the primary care level (the primary diagnosis), the final diagnosis made by the consultant neurologist (the definitive diagnosis) and the reason for referral were recorded.

The primary and definitive diagnoses were compared in order to determine which categories of cases referred did not have a change in the diagnosis as a result of the referral, and others that required assistance from a neurologist in reaching a conclusive diagnosis. The diagnosis was considered the same if the same diagnosis was made by both parties, or if the primary diagnosis was in the same broad category and the variance in diagnosis did not necessitate a change in management. If the management of the patient had to be altered, the primary diagnosis was regarded as provisional. For example, if the primary diagnosis was generalized epilepsy and the final diagnosis partial complex seizures, the primary diagnosis was provisional, even though both diagnoses lay within the broad category of epilepsy, because the therapy in each case would be different.

Statistical analysis

Assuming that the neurologist's diagnosis is the reference, positive predictive powers of the primary care physician's diagnoses were calculated for each diagnostic group. Chi-square test was used, as a "goodness of fit test", to assess the significance of the difference between the primary and definitive values. For fourfold contingency tables with expected frequency less than five, the Fisher's exact probability test was used.

Results

A total of 166 patients were referred to neurologists by the PCPs during the period of study. Of these, 114 (68.7%) were male and 52 (31.3%) were female. Their ages ranged from 12 to 82 years, the mean age and standard deviation of ages being 36.4 and 17.6 respectively. The most common conditions referred by the PCPs were epilepsies (31%), headaches (18%), diseases of the extrapyramidal and cerebellar systems (14%), spinal cord disorders (9%), peripheral nerve disorders (8%), and cerebrovascular accidents (7%).

Table 1 shows the primary diagnoses and the reason for referral. More than half of dementias, headaches, and spinal cord disorders were referred for further diagnostic evaluation or investigations. In almost one-quarter of the patients, the reason for referral was not stated. Cerebrovascular accidents and epilepsy were the ones largely referred for no clear reason although, as shown in Table 2, the primary diagnosis was invariably given and was in agreement with the neurologist's diagnosis in the majority of the cases.

The concordance of the primary and definitive diagnoses is shown in Table 2. The primary diagnoses in the categories of cerebrovascular accidents, epilepsy, space-occupying lesions, dementia, and extrapyramidal and cerebellar disorders showed a high agreement with the

TABLE 2. *The diagnostic accuracy of the primary care physicians compared with the specialists' diagnoses.*

Primary diagnosis	Total number of cases	No. of correct diagnoses	No. of incorrect diagnoses	Positive predictive value (%)
Cerebrovascular accidents	12	11	1	91.7
Epilepsy	51	44	7	86.3
Space-occupying disorders	6	5	1	83.3
Dementia	5	4	1	80.0
Extrapyramidal and cerebellar disorders	23	18	5	78.3
Headache*	30	20	10	66.6
Spinal cord disorders*	15	9	6	60.0
Peripheral nerve disorders†	14	7	7	50.0
Others	10	6	4	60.0
Total††	166	124	42	74.7

*=significant at 5% level; †=significant at 1% level; ††=significant at 0.1% level.

definitive diagnoses. Imprecise primary diagnoses occurred mainly in the categories of headaches, spinal cord disorders, and peripheral neuropathies as shown by their low positive predictive values. The differences in the primary and definitive diagnoses in the latter three categories were statistically significant ($P<0.05$).

Discussion

The patients compared in this study could have been unrepresentative of the entire spectrum of neurological disorders handled by the PCPs as a whole, since referrals are more likely to be confined to cases causing diagnostic or management difficulties or patients unresponsive or dissatisfied with their treatment.

Despite this, the results are encouraging as diagnostic agreement was found in nearly 75% of cases. There are no similar studies of diagnostic accord reported in the field of neurology. There are, however, recent studies that assess the diagnostic ability of PCPs in relation to psychiatry[13] and ophthalmology[14] in which the diagnostic concordance was 66% and 60% respectively. Therefore, it can be deduced that the overall diagnostic performance of PCPs in this study was very reasonable. However, some areas were identified in this study in which the diagnoses of the PCPs, even though largely correct, nevertheless required referral for a second opinion. This was especially the case with respect to headaches, spinal cord disorders, and peripheral neuropathies.

An enhancement of the primary care physicians" confidence in diagnosis could be achieved in these areas by increasing their knowledge and diagnostic skills in neurology. The undergraduate training should aim at recognition and differentiation of conditions commonly encountered in general practice.[10,15,16] Emphasis should be placed on the role of history taking and bedside skills to improve the performance of PCPs, especially in these stipulated areas.[12,17-20] The family physicians' needs may be served by block rotation in neurology, based on uniform content curriculum guidelines that are jointly developed by neurologists and family physicians.[21] These guidelines should also emphasize the interview and bedside examination skills, clinical knowledge, and correlative abilities as constituting the most powerful diagnostic tools for neurological disorders.[22]

An awareness of the complementary and mutually supportive roles of the PCPs and neurologists at this stage is essential. Primary care is a concept that consists of a set of tasks and responsibilities very different from principal care. All health care systems assume that specialists, including neurologists, can serve as principal care providers during certain episodes of illness.[4] Moreover, it is presupposed that a well-trained neurologist is best qualified to oversee the diagnosis and management of individuals with neurologic disorders.[23] Few would suggest, however, that all patients with any neurologic disorders should be treated solely by a neurologist.[24] The PCP is the patient's first contact. His role is to provide well-coordinated care, which is comprehensive and continuous, as well as promotive, preventive, curative, and rehabilitative for the patient and his family, regardless of the problem, be it biological, behavioral, or social.[4,25] Based on the above, in the presence of an effective primary care system, the neurologist's principal role would be to function as a consultant to PCPs and their patients.[4,24]

There are many other methods by which the diagnostic precision of the PCPs can be increased. An educational approach based on self and peer review can be very effective.[26] Training courses provided by faculty mentors who are community oriented and socially aware may be very useful. Optimal uptake can be achieved if these are learner centered with opportunities for small group discussion and hands-on experience and at times and places convenient to PCPs. Individual feedback on one's own performance in diagnosis and referrals (e.g., through audit of referral letters) is very helpful. It has been shown that following the introduction of individual feedback to general practitioners on their use of diagnostic tests, there has been a decrease in the number of requests for tests.[27,28] Providing feedback for the PCPs in this center on their high diagnostic accuracy and pointing out which cases they deemed to be diagnostically inadequate may direct attention to the type of cases requiring diagnostic referrals to the neurology outpatient clinic. The possibility of neurologists holding outpatient clinics in community settings can also be increased. This would have the advantage of feedback on a local level and would be particularly useful for physicians working in primary care centers distributed in the community. Finally, the development of locally agreed protocol for the diagnosis and management of those conditions common in general practice could greatly enhance the quality of professional performance.

The finding that many patients were referred without stating the reason of referral is worth examining. There could be covert reasons for referral. For example, a PCP being pressured by the patient or relatives might be motivated to pass contentious problems on or to obtain a second opinion.[29,30] In this case, physicians are encouraged to state their reasons clearly, as this would be more helpful to the neurologists[5,29] in identifying and responding to the needs of the PCP.

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APPARENT ABSENCE OF BCL-2 REARRANGEMENT IN TEN SAUDI FOLLICULAR LYMPHOMAS: A PRELIMINARY REPORT

Nargis Nasrin, PhD; Mohammed Akhtar, MD, FCAP;
Mohammed Ashraf Ali, MD, FRCPC, FCAP; Mohammed A. Hannan, PhD*

Specific chromosomal translocations are often found to be associated with distinct types of human neoplasms. The t(14;18) is considered to be a cytogenetic hallmark of the follicular lymphomas found mostly in American patients. This chromosomal translocation occurs through a 3' untranslated region (either major breakpoint region [mbr] or minor cluster region [mcr]) of the bcl-2 proto-oncogene in chromosome 18 and the JH region of the immunoglobulin (Ig) gene in chromosome 14. In the present study, the polymerase chain reaction (PCR) was used to detect a fusion DNA fragment generated from bcl-2/JH rearrangement either through mbr or mcr in 10 follicular lymphomas in Saudi Arab patients. Surprisingly, none of these cases showed any evidence of bcl-2 gene rearrangement through mbr or mcr. The absence of usual bcl-2/JH recombination in Saudi follicular lymphomas is intriguing and may suggest that the occurrence and mode of bcl-2 gene rearrangement in this lymphoma varies in different patient populations. *Ann Saudi Med 1994;14(3):219-224.*

In recent years, several types of chromosomal translocations resulting in specific gene rearrangement have been identified in human neoplasms.[1] In the hematolymphoid malignancies, the sites of the chromosomal translocation are clustered in those regions of the genome where certain cellular oncogenes are normally located. The most well-known example is t(9;22) through which the bcr/abl fusion gene characterizing Philadelphia chromosome in chronic myelogenous leukemia is produced.[2,3] C-myc is another proto-oncogene that is well studied in association with Burkitt lymphoma. In this tumor, c-myc translocates from chromosome 8 to heavy or light chain immunoglobulin loci as a result of t(8;14) or t(8;22) translocation respectively.[4,5] Several studies have demonstrated the occurrence of t(14;18) translocation in a majority of human follicular lymphoma.[6-11] Molecular biologic studies have shown that t(14;18) translocation juxtaposes the bcl-2 gene located on chromosome 18 to the transcriptionally active immunoglobulin heavy chain gene on chromosome 14 resulting in the deregulation of its expression. This translocation has been reported to occur most commonly through a major breakpoint region known as "mbr" and occasionally via a minor cluster region called "mcr" in the bcl-2 gene. The bcl-2 gene encodes a protein that prevents programmed cell death[12] and this gene product may thus protect certain lymphoma cells, giving them a survival advantage.

Some studies have shown that the frequency of t(14;18) in follicular lymphoma may vary considerably along geographic and ethnic lines. Its frequency may vary from up to 100% among the American follicular lymphoma to approximately 30% in the Japanese lymphoma.[13,14] There is little information available regarding the frequency of bcl-2 gene rearrangement in malignant lymphoma among the Saudi population. A study from King Faisal Specialist Hospital and Research Centre (KFSH&RC), to be reported elsewhere, on bcl-2 gene rearrangement in Saudi non-Hodgkin lymphoma (NHL) showed 67% of diffuse small cleaved cells (DSCC), 33% of diffuse large cells (DLC), and 33% of diffuse mixed small and large cells (DMSL) were positive for t(14;18) detectable by polymerase chain (PCR) technique.[15] In the present study, 10 Saudi follicular NHLs were analyzed specifically for bcl-2/JH recombination detectable by PCR. Surprisingly, none of these tumors showed bcl-2 gene rearrangement under the experimental conditions described in this preliminary report.

Material and Methods

Tumor Tissues and Classification

Tumor tissues from a total of 10 B-cell follicular NHLs (2 snap frozen and 8 paraffin embedded) were obtained from the Department of Pathology and Laboratory Medicine, KFSH&RC. Frozen samples were stored at -70°C until used. The diagnosis of lymphoma was based on conventional morphological examination of formalin and B5 fixed paraffin embedded tissue. In all cases,

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From the Departments of Pathology and Laboratory Medicine (Drs. Akhtar and Ali) and Biological and Medical Research (Drs. Nasrin and Hannan), King Faisal Specialist Hospital and Research Centre, Riyadh.

Address reprint requests and correspondence to Dr. Akhtar: Department of Pathology (MBC-10), King Faisal Specialist Hospital and Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia.

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immunohistochemical staining of frozen or B5 fixed tissue was performed. A mini panel including two pan B markers L-26 (Dako), Leu 14 (Becton Dickinson) and three Pan T markers UCL 1 (ENZO), CD3 (Dako), Leu 4 (Becton Dickinson) was used in order to determine B or T cell lineage of the lymphomas. Light chain restriction was determined by staining for kappa and lambda light chain (Biogen and Becton Dickinson). The histologic classification was performed by two pathologists (MA and MAA) based on the International Working Formulation.[16] All tumors that were diagnosed as follicular lymphoma revealed a prominent follicular pattern (Figure 1). In all cases, a prominent and follicular staining for L-26 was noted (Figure 2). Tumors with both follicular and diffuse areas were categorized as follicular lymphoma.

DNA Extraction and Polymerase Chain Reaction (PCR)

PCR was performed on genomic DNA extracted from snap frozen tissue following the method of Maniatis et al.[17] and from the paraffin embedded sections according to the protocol described by Wright and Monos.[18] Briefly, 2 µg of extracted DNA were added to 100 µl of 1xPCR buffer (10 mM TRIS pH 8.3, 50 mM KCl, 2.5 mM $MgCl_2$, 200 µM concentration of each deoxynucleotide, 0.02% gelatin), 2.5 units of amplitaq and approximately 100 pmols of each primer. The mbr or mcr primer was routinely used for chromosome 18 in a 40 cycle PCR. Universal JH consensus sequences were used for chromosome 14. Cycle conditions with JH and mbr primers were 60 sec at 92°C (denaturation), 60 sec at 68°C (annealing and chain elongation) with denatured step extended to four min at the beginning of the first cycle. For sequential amplification with JH and nested bcl-2 primers, annealing for one min at 55°C was used instead of 68°C. For mcr, the PCR reaction was carried out as above except that the cycle condition included 55°C annealing (two min), 72°C extension (one min) and 94°C denaturation (one min) for 30 cycles. The amplification was performed in a Perkin Elmer Cetus thermal cycler. The primer sequences were adopted from Kneba et al.[19] and Ngan et al.[20] which were 5'GCAATTCCGCATTTAATTCATGGTATTCAGGAT-3' for the mbr and 5'GACTCCTTTACGTGCTGGTACC-3' for the mcr respectively. The primers for the JH consensus region were: a) 5'GGTGACCAGGGTCCCTTGG-CCCCAG-3' used with the mbr primer (adopted from Kneba et al.) and b) 5'ACCTGAGGAGACGGTGACC-3' used with the mcr primer (adopted from Ngan et al.). Sequential amplifications were performed with an internal primer (5'CGTGGCCTGTTTCAA-3') for the mbr. Sequences from the bcl-2 gene comprising 5'-AACACAGACCCACCCAGAGCCCTCCTGCCCTCC TTCCGCGGGG-3' were used as a probe to Southern blot for mbr/JH fusion DNA segment. With each sample, a control experiment with the bcl-2 internal primers (purchased from ONCOR Science) was performed.

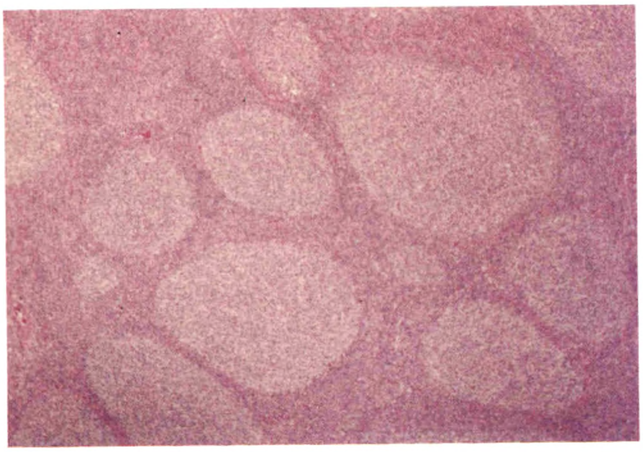

FIGURE 1. Photomicrograph showing a typical follicular lymphoma. Hematoxylin eosin staining - 100x.

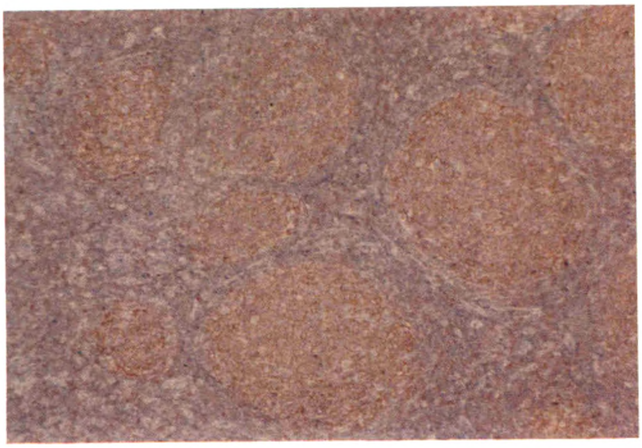

FIGURE 2. Photomicrograph showing prominent staining of the follicles by L26 immunoperoxidase staining - 100x.

Southern Blot Analysis of Genomic DNA

The DNA sample was digested with Hind III. The digested DNA was size-separated in 0.8% agarose gel and transferred to gene screen plus (NEN) membrane. The membrane was hybridized according to standard technique[17] and probed with mbr (1.2 Kb Oncogene Science) fragment of bcl-2 gene. The mbr probe was radiolabeled with ^{32}p dCTP (Amersham) by random priming (BRL). Autoradiographs were developed after seven days at -70°C. The mbr probe was tested using DNA from SU-DHL-6 cell line that has been previously shown to have a t(14;18) translocation.

Results

For positive bcl-2/JH translocation, the expected DNA band size is 300 to 350 bp when mbr and JH primers are used. We could not detect any positive bcl-2/JH translocation through mbr in any of the 10 cases of

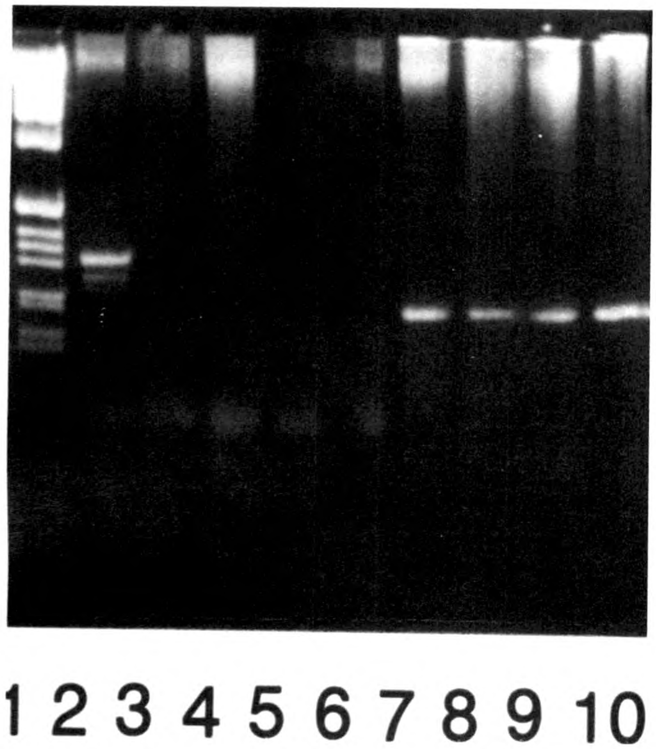

FIGURE 3. Ethidium bromide-stained 2% agarose gel of the PCR products synthesized using mbr/JH primers and follicular lymphomas DNA. Lane 1 - molecular weight marker; lane 2 - positive bcl-2/JH fusion gene products from DSCC NHL; lane 3-6 - PCR amplification of four follicular lymphomas; lane 7-10 - control bcl-2 gene segment using the same four follicular lymphomas DNA.

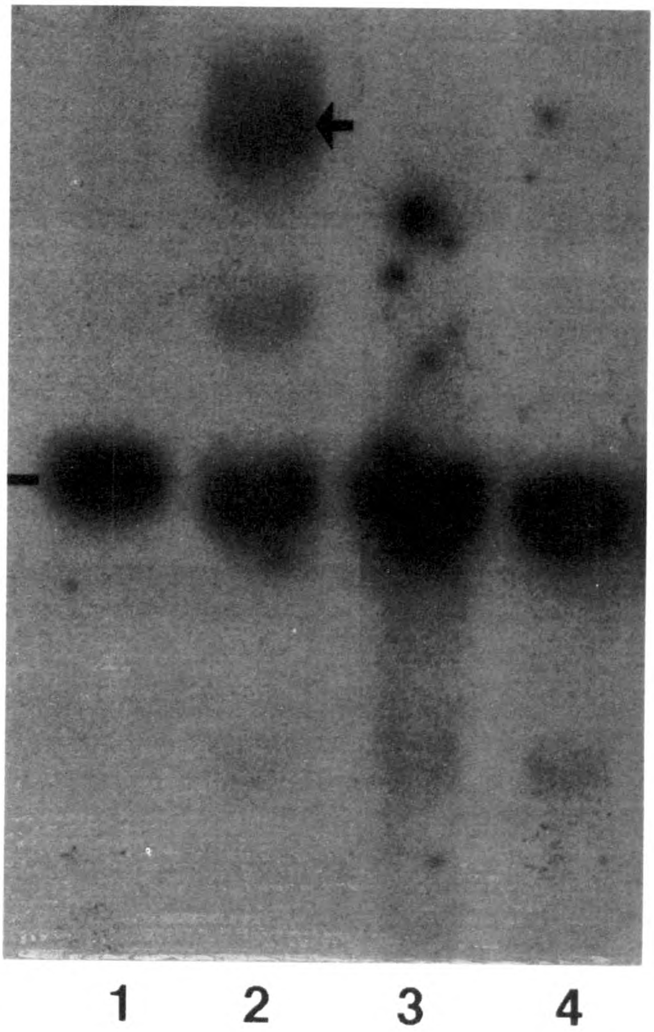

FIGURE 4. The results of Southern blotting of 10 μg DNA from patients with follicular lymphoma (lanes 3 and 4 show no rearranged bands for 2 follicular NHLs), negative control (placental DNA, lane 1) and a positive control (SU-DHL-6, lane 2). Hind III digested genomic DNA fragments were size separated and hybridized with mbr (1.2 Kb) DNA probe. Arrow shows the rearranged band whereas (-) shows the germline band.

follicular lymphoma studied (Figure 3). We also used mcr and consensus JH primers to further analyze the possibility of translocation through a minor cluster region. Again we could not detect any bcl-2 gene translocation through mcr and JH region (data not shown). It is interesting to note that we did not detect any t(14;18) via the mcr in any of the Saudi NHLs reported elsewhere.[15] To rule out the possibility of failure of PCR reaction, we used a positive t(14;18) DNA in every case (Figure 3) and used internal bcl-2 primers to generate a 220 bp fragment indicating the good quality of DNA used (Figure 3). Also, we carried out Southern analysis with DNA from frozen tissues of the two follicular lymphomas using the mbr probe and no evidence of bcl-2 rearrangement was observed (Figure 4).

Discussion

The bcl-2 gene is normally located on chromosome 18. It consists of three exons, the first of which is untranslated. The two coding regions are separated by 225 kb of DNA. A diagram of this gene is noted in Figure 5. The gene is oriented with the 5' end nearer the telomere and the 3' end nearer the centromere. Analysis of DNA from tumor cells known to have t(14;18) translocation shows that breaks may occur in two regions. The mbr, which is by far the most common, occurs within the second translated exon in the 3' untranslated region of the bcl-2 gene (Figure 5). The mcr occurs up to 20 kb downstream of this exon (Figure 5). There are some rare breakpoints scattered in various sites flanking bcl-2 either at 5' or 3' ends. Recently, there have been reports of variant translocations involving bcl-2 such as t(2;18) and t(18;22) in follicular lymphomas.[21] The positions of breakpoints are illustrated in Figure 6. In most of the published studies on bcl-2 gene translocation, only probes for mbr and mcr have been used. A few researchers have described positive results with probes for breakpoints at 5' region of the bcl-2 gene.

Weiss et al.[6] and Gulley et al.[13] reported that 89% to 100% of the American follicular lymphomas showed bcl-2 rearrangement through mbr and mcr. However, studies from other countries indicate that the frequency of bcl-2 gene rearrangement in NHLs may be extremely variable.

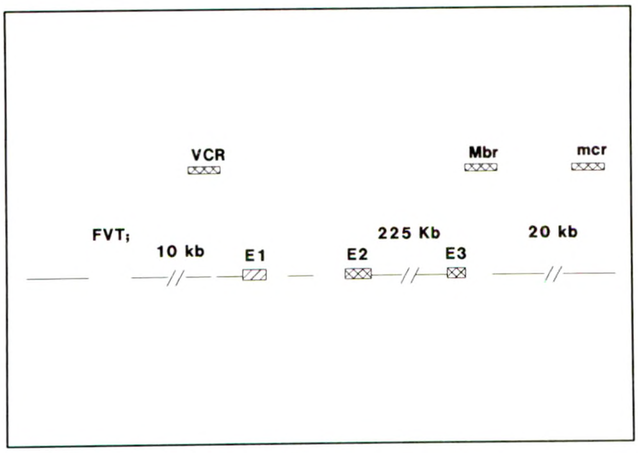

FIGURE 5. Schematic representation of the bcl-2 gene on chromosome 18. The gene consists of three exons;[31] the coding exons are indicated by cross hatched box. The variant cluster region (VCR), the major breakpoint region (mbr) and minor cluster region (mcr) are shown at the appropriate position of the bcl-2 gene. On rare occasion, follicular lymphoma is reported to be translocated through follicular variant translocation (FVT) site that is located 5' of the VCR. (This figure is adopted from Bertheas et al.[21])

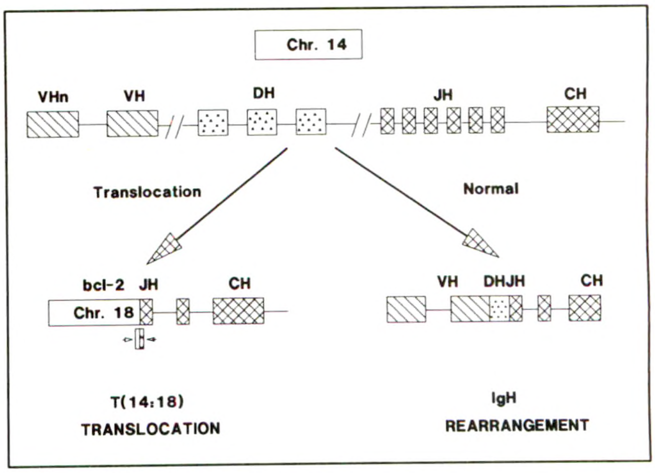

FIGURE 6. Schematic representation of strategy for PCR amplification of t(14;18) translocation involving the bcl-2 oncogene (chromosome 18) and JH region of the immunoglobulin heavy chain gene (chromosome 14) using primers. The small arrows indicate the location of the mbr and JH universal primers. (This figure has been adopted from Corbally et al.[34])

For example, Pezzella et al.,[22] in a series of 51 follicular lymphomas, found bcl-2 rearrangement in less than 50% of the cases. Interestingly, in this study, follicular lymphoma from the United Kingdom had a lower frequency of bcl-2 rearrangement (26.3%) as compared to those from Denmark (61.5%). In a series of Japanese follicular lymphomas, Amakawa et al.[14] reported the occurrence of bcl-2/JH fusion only in 30% of the cases. Results from several studies are summarized in the table. These results indicate that, of all the follicular lymphomas from different countries, bcl-2 rearrangement was present in 33% to 100% of the cases analyzed. By contrast, the results from our study failed to reveal bcl-2 translocation in any of the follicular lymphomas through mbr (Figure 3) and mcr. The reason for this apparent discrepancy is not clear, although the small number of cases studied may be a significant factor. Also, we cannot rule out rearrangement through various cluster regions (VCR) or variant translocations such as t(2;18) and t(18;22) in Saudi follicular lymphomas. The only other study in which a complete absence of t(14;18) was noted was published from Russia.[23] In this study, all 10 follicular lymphomas studied by cytogenetic analysis failed to detect t(14;18). The data shown in the table strongly suggest the existence of a geographic variation in the frequency of bcl-2 gene rearrangement in follicular NHLs irrespective of the methods of detection used.

Malignant lymphoma is one of the most common neoplasms in Saudi Arabia.[24,25] The various subtypes of malignant lymphoma in Saudi Arabia are essentially similar to those seen in many other countries. However, the relative proportion of follicular lymphoma is extremely low. In a study of 211 malignant lymphomas published from our laboratory, only six (3%) follicular lymphomas were encountered.[26] This is in sharp contrast to the studies published from the Western countries where the follicular lymphoma may represent up to 50% of the malignant lymphomas. In other regions such as Japan and Hong Kong, follicular lymphomas constitute only 19% and 13.2% of the malignant lymphomas respectively.[14,27] It is not clear whether or not there is any relationship between the relative frequency of follicular lymphoma and the incidence of bcl-2 translocation in different populations.

The bcl-2 gene translocation is not limited to follicular lymphoma and may be present in a variable proportion in other B-cell lymphomas, especially the group of follicular center cell lymphomas. These include diffuse small cleaved, diffuse mixed, diffuse large cell, and diffuse small noncleaved cell lymphomas. Of these, the diffuse small cleaved cell lymphoma has the highest frequency of bcl-2 gene rearrangement, followed by diffuse mixed and diffuse large cell lymphomas. In a study of 57 B-cell lymphomas analyzed by Southern blot and PCR, Gulley et al.[13] found the evidence of bcl-2 gene translocation in 100% of follicular small cleaved cell lymphomas, 67% of diffuse small cleaved cell lymphomas, 33% of mixed cell lymphomas, 25% of diffuse large cell lymphomas and 25% of small noncleaved cell lymphomas. In another study, 19 out of 102 cases of diffuse large cell lymphomas were found to have bcl-2 gene rearrangement.[28] In a study using identical methods (to be reported elsewhere), we observed bcl-2 translocation in eight of 12 (67%) diffuse small cleaved cells, one of the three (33%) diffuse mixed and one of 11 (9%) diffuse large cell lymphomas, which appeared to be consistent with reports from other laboratories.[19] However, the total absence of t(14;18) resulting in bcl-2/JH fusion DNA via mbr or mcr in Saudi follicular NHLs described in the present report is intriguing and warrants

TABLE: *Frequency of bcl-2 gene rearrangement in follicular lymphomas reported in the literature using molecular biology techniques (Southern blot or polymerase chain reaction).*

Author	Ref	Year	Country where study was conducted	Method used	Number of cases studied	Number of cases positive for mbr	Number of cases positive for mcr	Total	%
Amakawa et al.	[14]	1989	Japan	Southern	30	8	2	10	33
Aisenberg et al.	[29]	1988	USA	Southern	37	11	ND	11	30
Weiss et al.	[6]	1987	USA	Southern	36	21	11	33	89
Tsujimoto et al.	[30]	1987	USA	Southern	18	11	ND	11	61.1
Lipford et al.	[31]	1987	USA	Southern	17	11	ND	11	65
Lee et al.	[32]	1987	The Netherlands	Southern	19	14	ND	11	73.7
Pezzella et al.	[22]	1990	United Kingdom	Southern/PCR	38	10	1	11	28.9
Pezzella et al.	[22]	1990	Denmark	Southern/PCR	13	8	2	10	76.9
Loke et al.	[27]	1990	Hong Kong	Southern	16	8	1	9	56.2
Benitez et al.	[33]	1991	Spain	Southern/PCR Cytogenetics	5	3	None	3	60
Gulley et al.	[13]	1992	USA	Southern	6	5	1	6	100
Present study				Southern/PCR	10	None	None	None	0

PCR=polymerase chain reaction; mcr=major breakpoint cluster region; mbr=major breakpoint region.

further studies with larger series and Southern blotting to confirm this observation or find alternative mechanisms of bcl-2 rearrangement, if any. It is particularly surprising that the use of similar procedures enabled the detection of bcl-2/JH recombination in two-thirds of the Saudi diffuse small cleaved cell NHLs but in none of the 10 follicular ones, while these are believed to be closely related pathogenetic entities.

Worldwide experience with bcl-2 oncogene translocation is expanding at a rapid pace. This is contributing to greater understanding of the histogenesis and pathogenesis of B cell lymphomas. This information is also expected to contribute to a precise and more meaningful classification of these lymphomas. Our findings in this study, if confirmed, may have significant implications for the current concepts regarding follicular lymphoma and its relationship to other B cell lymphomas with respect to the mechanism(s) of bcl-2 rearrangement. Further studies using mbr, mcr and 5'bcl-2 probes to analyze tissue DNA from numerous follicular NHLs by both PCR and Southern blot techniques will be needed to establish the infrequency of bcl-2 rearrangement in Saudi follicular lymphomas.

Acknowledgment

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A CLINICOEPIDEMIOLOGIC STUDY OF HEART DISEASE IN SCHOOLCHILDREN OF MENOUFIA, EGYPT

Mamdouh Refat, MD; El Saeed Rashad, MD; Farahat A. El Gazar, MD;
Ali M. Shafie, MD; Mohammad M. Abou El Nour, MD; Ahmad El Sherbini, MD;
Mohammad K. El Soubky, MD; Ahmad M. Eissa, MD

This study was conducted to determine the prevalence of rheumatic heart disease (RHD) and congenital heart disease (CHD) in primary schoolchildren of Menoufia, Egypt and to study the relationship between these two problems and socioeconomic conditions. A total of 8000 children were screened for cardiac disease in their schools. Children with confirmed RHD and CHD in addition to 200 healthy children (controls) were visited at their homes to assess their social environment and other factors according to a designed questionnaire. We found prevalence rates of 3.4/1000 and 2.6/1000 for the RHD and CHD respectively. The most common cardiac defects were double mitral and pulmonary stenosis in the RHD and CHD groups respectively. Nineteen (39.6%) of the patients were diagnosed for the first time during the study. Penicillin prophylaxis was received by only four (14.8%) of the RHD children and none of the CHD children. The number of other affected siblings, increased multiparity, repeated abortion, and intake of contraceptives by mothers were significantly higher in families of the children with CHD. The proportion of illiterate, unskilled, and heavy smoking fathers was higher in the two patient groups. Family income was lowest in the RHD group, while increased crowding index and low whole social environment were significantly related to both RHD and CHD. Effective programs at the community and health service levels are needed in Menoufia to solve the problem of heart disease in schoolchildren in the immediate future. *Ann Saudi Med 1994;14(3): 225-229.*

Rheumatic and congenital heart disease are still significant causes of morbidity and mortality in Egyptian children.[1,2] Likewise, the incidence of rheumatic fever (RF) and the prevalence of rheumatic heart disease (RHD) in developing countries remain high[3] due to poor living conditions and limited medical services.[3-5]

On the other hand, there is little information on the prevalence of congenital heart disease (CHD) in school-age children in Egypt. Environmental factors are said to play a major role in modulating the genetic predisposition to this problem[6,7] and community-based surveys are needed to identify those risk factors.

Early school surveys of RHD[8-10] and hospital studies of CHD[2] were conducted in Egypt. However, recent community-based data are needed to define the magnitude of the problem of heart disease in children in order to develop effective medical services and control measures. This study was conducted to determine the prevalence of rheumatic and congenital heart disease in primary schoolchildren in Menoufia, Egypt and to assess the relationship between these two problems and socioeconomic and other risk factors.

Subjects and Methods

Menoufia governate lies 75 km from Cairo, Egypt with a population of approximately two million, the majority of whom are farmers and workers, and is divided into five urban-rural areas. Out of the 200,000 children attending compulsory primary schools in the governate, 8000 were chosen in this study by proportionate allocation method.[11] These 8000 children represented all the children registered in 14 schools, which were selected based on their population size to provide the sample size required and to represent the five areas of the governate. This study was conducted from September 1990 to April 1991 and consisted of clinical and epidemiological surveys.

Clinical Survey

In this part, the selected schools were visited by a team consisting of three pediatricians. All children attending on the visit day were examined by members of the team who focused on cardiac examination. Children judged by at least two examiners to have established or suspected heart disease were referred to the Menoufia University Hospital. Further, children registered in the school as having heart disease, who were absent on the visit day, were left a referral note to go to the hospital. In the hospital, children

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From the Departments of Pediatrics (Drs. Refat, Rashad, El Gazar, Shafie, Abou El Nour), Community Medicine (Drs. El Sherbini, El Soubky) and Pediatric Cardiology (Dr. Eissa), Menoufia Faculty of Medicine, Menoufia, Egypt.

Address reprint requests and correspondence to Dr. Refat: Consultant of Pediatrics, King Fahad Hofuf Hospital, Al Hassa, Saudi Arabia.

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were subjected to detailed history obtained from the parents as well as examination by a pediatric cardiologist and to the following investigations: chest x-ray, electrocardiogram, echocardiogram (M-mode and 2D) and color Doppler (CW, PW, CD, CFM, HP-Sono 500, USA). According to history, physical examination, and investigation, children with innocent murmur and those who proved to be free from heart disease were excluded from the study and those with confirmed heart disease were classified into congenital heart disease (CHD) (Group 1) and rheumatic heart disease (RHD) (Group 2). The diagnosis in the first group was based on a history of illness since early infancy in the majority of cases, on murmur characteristics, x-ray and echocardiogram findings. RHD was diagnosed based on previous history of rheumatic fever, when reported, multiplicity and nature of valvular cardiac defects, and echocardiographic findings. Children in this group were further subjected to determination of erythrocyte sedimentation rate, anti-streptolysin-0 titer, and C-reactive protein to rule out possible recent rheumatic activity.

Epidemiological Survey

In the second part of the study, all children with documented heart disease were visited at their homes by two members of the team. Two hundred healthy children, chosen by simple random sampling from the study schools, were included in this part as the control group (Group 3). Randomization of this group was proportional to the number of diseased children in each school. The purpose of home visits was to assess the socioeconomic conditions of all the children according to a scoring system[11] derived from a designed questionnaire inquiring about extra and intrafamilial data.

Statistical Analysis

The three groups were compared regarding the scores of their clinical and socioeconomic data using frequency tables, t-test, X, F and Z tests where applicable. A *P* value <0.05 was considered significant.

Results

A total of 8000 children (4150 males and 3850 females, six to 12 years of age) were screened for cardiac abnormalities in their schools. Out of 281 children referred to the hospital, 167 were diagnosed as having innocent murmur and 66 proved to be free from cardiac problems (39 and 27 were initially suspected as having RHD and CHD respectively) and were excluded from the study. RHD was diagnosed in 27 children and CHD was detected in 21 children, making prevalence rates of 3.4/1000 and 2.6/1000 respectively (Table 1). Older children (10 to 12 years) had higher RHD prevalence than younger ones while CHD was detected in female more than male children. None of the RHD children showed clinical or laboratory evidence of rheumatic activity and none of the children in either group were suffering from any acute complications at the time of the study.

The most common cardiac lesion detected in the RHD group was double mitral (DM) followed by isolated mitral regurgitation (MR), while valvular pulmonary stenosis (PS) followed by ventricular septal defect (VSD) were the most common lesions diagnosed in the CHD group (Table 2). Based on echocardiogram and Doppler, rheumatic defects were mild in nine (33%) of the children, moderate in four (15%) and severe in 14 (52%); congenital lesions were mild in 12 (57%), moderate in seven (33%) and severe in two (10%) of the children.

Nineteen (39.6%) of the 48 cardiac children were not diagnosed before the present survey. Of these, seven were among the first group [MR (3), MS (2), DM (2)] and 12 belonged to the second group [PS (4), VSD (3), ASD (3), MVP (1) and PDA (1)]. In the RHD group, a history of rheumatic fever was elicited in only 10 (37%) children, two of whom had two recurrent attacks. None of the children were subjected to throat swab during attacks of sore throat or RF. Four (14.8%) of the children with RHD

TABLE 1. *Number of patients examined and prevalence /1000 of rheumatic heart disease (RHD, group 1) and congenital heart disease (CHD, group 2) according to age and sex.*

	Group I (RHD)		Group II (CHD)		Total no	
	No.	Prevalence	No.	Prevalence	examined	(%)
Age (years)						
6 - <8	5	1.5	6	1.8	3280	(41%)
8 - <10	6	2.4	8	3.2	2480	(31%)
10-12	16	7.1	7	3.1	2240	(28%)
Sex						
Male	11	2.7	6	1.4	4150	(51.9%)
Female	16	4.2	15	3.9	3850	(48.1%)
Total	27	3.4	21	2.6	8000	

P values for both age and sex were >0.05; RHD=rheumatic heart disease; CHD=congenital heart disease.

TABLE 2. *Types and percent of cardiac lesion in the study groups.*

RHD Group			CHD Group		
Lesion	No. (total no. = 27)	(%)	Lesion	No. (total no. = 21)	(%)
DM	12	(44.4%)	PS	7	(33.3%)
MR	5	(18.5%)	VSD	4	(19%)
MS	4	(14.8%)	ASD	4	(19.0%)
DM+AoR	3	(11.1%)	AoS	3	(14.3%)
DM+DAo	2	(7.4%)	PS+VSD	1	(4.8%)
DM+DT+PR	1	(3.7%)	MVP	1	(4.8%)
			PDA	1	(4.8%)

DM=double mitral; MR=mitral regurgitation; MS=mitral stenosis; AoR=aortic regurgitation; DAo=double aorta; DT=double tricuspid; PR=pulmonary regurgitation; PS=pulmonary stenosis; VSD=ventricular septal defect; ASD=atrial septal defect; AoS=aortic stenosis; MVP=mitral valve prolapse; PDA=patent ductus arteriosus.

TABLE 3. *Maternal risk factors.*

Risk factor	Group 1 (RHD) (No.=27) No.	(%)	Group 2 (CHD) (No.=21) No.	(%)	Controls (No.=200) No.	(%)
Parity						
<5th	5	(18.5%)	5	(23.8%)	45	(43.5%)
>5th	22	(81.5%)	16	(76.2%)	113	(56.5%)
Stillbirth	0		3	(14.3%)	3	(1.5%)
Abortion	6	(22.5%)	13	(61.9%)	42	(21%)
Drugs	1	(3.7%)	4	(19%)	8	(4.0%)
Hormones	2	(7.4%)	5	(23.8%)	12	(6.0%)
Trauma	0		2	(9.5%)	0	

*=p=0.05 (groups 1 and 2 versus controls); **=p=0.05 (group 2 versus group 1 and controls); RHD=rheumatic heart disease; CHD=congenital heart disease.

were taking a regular monthly injection of long-acting penicillin, two (7.4%) were taking the drug irregularly and 21 (77.8%) were not receiving any prophylaxis. None of the CHD children were given prophylaxis against bacterial endocarditis when it was indicated.

Regarding family history, consanguinity was higher but not statistically significant in only the CHD group compared to the control group, while birth order of the affected child did not differ much between the three groups (data not shown). In seven (33.3%) families of the children with CHD, there were one or more siblings affected with CHD and the difference, compared to the controls, was statistically significant ($P<0.001$), 6 (22.2%) and 17 (8.5%) children in the RHD and control groups respectively have one or more other siblings affected with RHD ($P>0.05$).

Table 3 presents results of comparison of the maternal risk factors among the three groups. High multiparity (more than five pregnancies) was statistically higher in Groups 1 and 2 than in the controls ($P<0.05$). History of previous stillbirth and repeated (more than twice) abortion was reported more frequently by mothers of the CHD children than in the other two groups ($P<0.05$). Likewise, 23.8% of mothers of the CHD children gave a history of taking contraceptive pills during early pregnancy (by mistake) compared to 7.4% and 6% in mothers of RHD and control children respectively ($P<0.05$).

In terms of socioeconomic conditions, for each social variable a score was calculated and compared between the two study groups and then to the control group, and the results are summarized in Tables 4 and 5. Parents' age and maternal education and occupation did not differ in the three groups, while the proportion of less educated and unskilled fathers was higher in the RHD and CHD groups than in the controls. The scores of smoking habits of the fathers in the two patient groups were statistically higher than in the controls. In the RHD group, the score of family income was much less than in the control group; the CHD group did not show the same result.

As shown in Table 5, no major differences were observed with respect to housing conditions except crowding index, water supply, and sewage and refuse disposal among the three groups. Conversely, score of roads, residential units, and combined environmental conditions were lower, and crude crowding index was higher in Groups 1 and 2 than in the controls ($P<0.05$). However, there were no significant differences in these variables between the RHD and CHD groups, though the scores were slightly less in the RHD group.

Discussion

The prevalence of RHD in schoolchildren varies considerably throughout the world.[3] It has been reported as 0.6/1000 in the USA[12] and 0.7/1000 in Japan,[13] while in developing countries, prevalence rates ranging from 0.3/1000 to 18.6/1000 have been reported.[3] Our rate (3.4/1000) is high compared to rates found in industrialized countries, and is also higher than figures reported from some areas in the developing world, as in Cote d'Ivoire (1.9/1000), Nigeria (0.3/1000), Uruguay (1.0/1000) and China (0.4/1000).[3] It appears also that schoolchildren in Menoufia have a higher rate than those found earlier in other areas of Egypt where prevalence rates of 1.3/1000 in the Western Desert Coast[8] and 0.7/1000 in Alexandria[10]

TABLE 4. *Mean standard deviation (SD) of scores of social variables in patients and controls.*

Social variable	RHD group (No.=27)		CHD group (No.=21)		Controls (No.=200)		p value
Father's age	2.21	(1.38)	2.37	(1.26)	2.58	(1.40)	b;d;f;h.
Mother's age	2.45	(1.41)	2.58	(1.43)	2.74	(1.29)	b;d;f;h.
Father's occupation	1.29	(0.95)	1.47	(0.94)	2.04	(0.94)	a;c;f;h.
Mother's occupation	1.02	(0.68)	1.13	(0.67)	1.24	(0.67)	a;c;f;h.
Father's education	1.83	(0.82)	1.84	(0.69)	2.82	(1.1)	a;c;e;h.
Mother's education	1.46	(1.0)	1.39	(0.98)	1.81	(0.91)	b;d;g;h.
Father smoking	3.13	(1.7)	3.1	(1.59)	3.83	(1.45)	a;c;e;h.
Family income	2.25	(0.74)	2.58	(0.77)	2.98	(0.90)	a;c;f;h.

*=result of p value; a & b significant & insignificant between the 3 groups, respectively; c & d significant & insignificant between RHD group & control, respectively; e & f significant & insignificant between CHD group & control, respectively; j & h significant & insignificant between RHD & CHD groups, respectively; RHD=rheumatic heart disease; CHD=congenital heart disease.

TABLE 5. *Mean standard deviation (SD) of environmental factors and crowding index in patients and controls.*

Variable	RHD group (No.=27)		CHD group (No.=21)		Controls (No.=200)		*p* value
Roads	6.31	(1.36)	7.09	(1.33)	7.16	(1.41)	a,c,f,j.
Housing condition	8.77	(2.86)	9.76	(2.71)	9.84	(2.99)	b,d,f,h.
Water supply	2.41	(1.31)	3.19	(1.21)	3.36	(1.12)	b,d,f,h.
Sewage disposal	3.59	(0.69)	3.85	(0.79)	3.84	(0.92)	b,d,f,h.
Refuse disposal	1.42	(0.72)	1.32	(0.75)	1.73	(0.87)	b,d,f,h.
Residential units	14.75	(5.4)	16.26	(4.9)	17.72	(4.7)	a,c,f,h.
Whole social factors	21.87	(5.3)	23.05	(5.5)	28.02	(5.5)	a,c,e,h.
Crowding index	3.03		2.31		1.92		a,c,e,h.

*=result of *p* value; a & b significant & insignificant between the 3 groups, respectively; c & d significant & insignificant between RHD group & control, respectively; e & f significant & insignificant between CHD group & control, respectively; j & h significant & insignificant between RHD & CHD groups, respectively; RHD=rheumatic heart disease; CHD=congenital heart disease.

were reported. Further, children with severe RHD are likely to drop out of school and this may have underestimated the true prevalence of RHD in the present survey. However, there were no medical records for those children in the schools visited.

The high prevalence of RHD in Menoufia schoolchildren could largely be attributed to the low standard of living found in their families. Our children with RHD have the lowest scores of social environment and the highest crude crowding index compared to the other groups (Tables 4 and 5). The decline in the prevalence of RHD in industrialized countries has largely been attributed to the improvement in the standard of living,[14] and the persistence of this major public health problem in developing countries is mainly due to of low social circumstances and poverty.[3,15] The low scores of education, income and occupation of the head of the family in the RHD group have previously been observed in studies of RHD prevalence.[16-18] Poverty and illiteracy breed overcrowding, which promotes the spread of many infections which, due to ignorance and scarcity of health facilities, are often neglected until complications set in, as in RF.[15,17,18]

Previous studies of the incidence of affected valves in RHD have reported the mitral valve as the most common valve affected[4,19] and this is consistent with our findings (Table 2). Unfortunately, combined MR and MS found in the majority of our children are said to favor the onset of bacterial endocarditis.[20] Furthermore, severe and multiple valvular damage as observed in our children indicates previous severe attack of rheumatic carditis and is more common in children of developing countries than those of developed countries.[16]

Failure to initiate and/or comply with penicillin prophylaxis was found in more than half of our RHD children and similar findings have previously been reported in Egypt[18] and in other countries.[4,19] Factors contributing to failure of penicillin prophylaxis include: children not subjected to throat culture during throat infection, seven patients not diagnosed before the study, fear of penicillin, illiteracy of some parents, and inadequate medical supervision. It has been shown that the natural history of RF can be dramatically altered by effective penicillin prophylaxis at different points of the disease.[3,20-22]

There is little information on the prevalence of CHD in schoolchildren in Egypt. The prevalence found in this study (2.4/1000) is not markedly different from rates reported from other areas of the world.[23-25]

A hereditary predisposition for cardiac anomalies together with an environmental trigger during early pregnancy is currently the most accepted explanation for the cause of CHD.[6,7] In the present study, the high percentage of consanguineous marriage, other siblings affected, stillbirth and abortion in families of the CHD children may reflect a hereditary predisposition for the cardiac defects. On the other hand, high multiparity, drug abuse during pregnancy, maternal trauma, father smoking and low score of the whole social environment found in the CHD families (Tables 3 and 4) may be contributing environmental factors to the occurrence of CHD. However, these findings should be interpreted with caution since maternal history of exposure to environmental risk factors during previous pregnancy may be biased by maternal memory. Another study is needed in the same area and at the time of birth to evaluate the relationship between environmental factors and the occurrence of CHD. Several previous studies have observed that both hereditary and environmental risk factors are associated with CHD.[2,6,7,26,27]

The finding of PS and not VSD as the most common congenital cardiac lesion and the deficiency of cyanotic defects in our children may be accounted for by the following: 1) many small VSDs close spontaneously before reaching school age; 2) PS was of mild degree and this favors good prognosis; 3) cyanotic lesions may not be seen in our age group or may result in school dropout; and 4) the incidence of individual CHD lesions may be influenced by racial genetic factors.[28]

A significant number of our children were not diagnosed prior to this study. Mild symptoms of some defects, inadequate medical supervision and unavailability of echocardiogram may explain this finding. However, unless community-based surveys are undertaken, many children with heart disease go undetected.[3] Early detection and treatment produce better long-term results for these children and there should be increased attention to cardiovascular examination in routine checkup of schoolchildren. In addition, late diagnosis and lack of a previous history of RF in the majority of our RHD children emphasize the importance of primary penicillin prophylaxis in children with streptococcal sore throat.[3]

In conclusion, the prevalence of heart disease in schoolchildren of Menoufia is high. This may be related to low socioeconomic level and other environmental risk factors, particularly where RHD is concerned. Improving the standard of living of the community and especially overcrowding in Menoufia is essential for long-term prevention of this problem. However, practical programs at the community and health service levels are needed in the immediate future. At the community level, these programs should focus on education of the general population on the importance of prophylaxis against rheumatic fever and on the importance of antenatal care and avoiding risk factors associated with the occurrence of heart disease. At the level of health services, rheumatic fever prevention programs should be implemented in Menoufia, guided by reliable and recent community-based data. In addition, promotion of the availability of cardiac ultrasound and trained personnel in the local hospitals is needed for the early diagnosis and treatment of heart disease in schoolchildren and the creation of medical records for follow-up of the cases detected.

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PREVALENCE OF TOXOPLASMA ANTIBODIES IN BLOOD DONORS IN AL-HASSA

Art Yaneza, FRCPath; Prasanna Kumari, MD

Toxoplasmosis is caused by an obligate intracellular protozoan parasite, *Toxoplasma gondii*. Most of the toxoplasma infections are asymptomatic or benign, but may cause severe or fatal consequences in immunodeficient patients, transplant recipients, and in the fetus. Transmission may occur by eating uncooked meat, contaminated vegetables, blood transfusion, organ transplantation, and across the placenta from the mother to the fetus. Antibodies to *T. gondii* may persist in the serum at high titers for years. We screened 784 Saudi blood donors using indirect hemagglutination test and 294 (37.5%) were found to be seropositive at different titers. The highest rate of seropositivity was found in the age group 21 to 30 years in males, and after 40 years of age, the presence of antibodies declined. Among females, the higher rate of seropositivity in the age group 18 to 20 years should be confirmed by further studies. *Ann Saudi Med 1994;14(3):230-232.*

Toxoplasmosis caused by an obligate intracellular protozoan parasite *Toxoplasma gondii* is a very common infection among young adults in different parts of the world.[1] Most of the toxoplasma infections are either asymptomatic or otherwise benign, but in some fetuses, patients with acquired immunodeficiency syndrome (AIDS), transplant recipients, and in patients receiving cytotoxic therapy, they may cause severe or even fatal consequences.[2] Of those patients with AIDS who are seropositive, about 25% to 50% will develop toxoplasmic encephalitis.[3] Transmission to the fetus occurs when the mother acquires acute infection during pregnancy. The disease may be transmitted by blood transfusion.[2] It is difficult to distinguish between the recently acquired infection and the chronic infection because of the frequent presence of toxoplasma antibodies in the general population.[4] These antibodies may persist in the serum of an asymptomatic individual for years at high titers.[5] In this study, sera from 784 Saudi blood donors at King Fahad Hofuf Hospital were screened for toxoplasma antibodies and 294 (37.5%) of them were found to have antibodies to toxoplasma at different titers.

Material and Method

Blood from Saudi donors at King Fahad Hofuf Hospital was randomly collected for the study. The sera were separated and stored in aliquots at -10°C for about a month. The total number of donors screened was 784, of which 750 were males and 34 were females. The age of the donors ranged from 18 to 50 years. The sera were inactivated at 56°C for one hour and an indirect hemagglutination test using Toxocell-IHA (Biokit, Spain) was performed according to manufacturer's instructions. Each sera was diluted from 1/16 up to 1/128. Any serum with a titer of 1/128 was further diluted up to 1/8192. Sera showing nonspecific agglutination were absorbed and retested. The absorbent reagent containing stabilized and unsensitized sheep cells at a cellular concentration of 10% and resuspended in a pH 7.2 buffer solution with stabilizing agent is provided in the kit. Absorption of nonspecific agglutinins was done by mixing the undiluted test serum with the absorbent reagent and incubating at room temperature for one hour and then centrifuging it. The supernatant was used to make further dilutions and tested qualitatively and quantitatively as discussed above. A positive and a negative control sera and an antigen control were included in each batch of tests.

Results

Out of 784 sera tested, 294 (37.5%) were found to be positive for toxoplasma antibodies. There were 279 (35.6%) males and 15 (1.9%) females. Of the seropositive, 94 (34.7%) of the males and 10 (66.7%) of the females had a titer of 1/16. Five (1.74%) males had a titer of 1/2048 and one (0.35%) had a titer of 1/8192. Among the female donors, one (6.6%) had a titer of 1/1024.

Among males, the highest detection of antibodies is in the age group 21 to 30, 132 (48.01%); followed by 18 to 20, 69 (24.7%); and 31 to 40, 58 (20.7%). The lowest seropositivity is in the age group 41 to 50, 20 (7.16%). Among the females, the highest seropositivity is in the age group 18 to 20 years, 6 (40%); followed by 21 to 30, 4

From the Department of Microbiology, Al-Hofuf, Al-Hassa.

Address reprint requests and correspondence to Dr. Yaneza: Microbiologist, King Fahad Hofuf Hospital, Al-Hofuf, Al-Hassa, Saudi Arabia.

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(26.6%); and 31 to 40, 3 (20.0%). The lowest antibodies recorded were in 41 to 50, 2 (13.3%).

Discussion

The protozoan parasite, *Toxoplasma gondii*, is transmitted to man by ingestion of the tissue cysts in raw or undercooked meats, particularly lamb and pork, or contact with cat feces.[6]

Intrauterine transmission occurs in approximately 25%, 54%, and 65% of untreated pregnant women who develop acute toxoplasmosis during the first, second, and third trimesters respectively. Specific maternal therapy can reduce the overall incidence of fetal infection by 50%. Fetal involvement is most severe when maternal infection is contracted early in pregnancy.[2]

In immunodeficient patients such as those with AIDS or receiving immunosuppressive and cytotoxic therapy, the infection is usually due to reactivation and dissemination of latent infection. In organ transplant recipients, it may be acquired through the transplanted organ if the donor is seropositive. The parasite can survive in stored blood at 4°C for up to 50 days.[2] Hence, there is a risk of transmitting the infection to recipients. This risk may be reduced by obtaining seronegative donor blood for transfusion.

The prevalence of toxoplasma antibodies ranges from 5% to 95% among young adults in different parts of the world. In the United States, by the end of the fifth decade of life, approximately 50% of the population are asymptomatically infected.[1] In our study, the prevalence of toxoplasma antibodies among apparently healthy blood donors was 37.5% by IHA test. Similar surveys conducted in Scotland, United Kingdom among the general population showed a rate of only 27% using the dye test[7] and that in Kenya showed 54% by hemagglutination test and 42% by the dye test.[8] In a study from Jordan, 37% were seropositive among women using IHA test[9] and Ferraroni et al.[10] have used IHA test to detect toxoplasma antibodies in men in the Amazon basin and found 59% to be positive. The exact incidence of toxoplasma infection with subclinical infection or with overt disease in Saudi Arabia is not known. One study employed toxoplasma skin test to find evidence of toxoplasma latent infection in symptomatic and asymptomatic populations in Riyadh, Saudi Arabia and the overall positivity was found to be 21%.[11] A study from Scotland and England in rural and urban blood donors showed 7.6% and 7.8% seropositivity[12] respectively, which is much lower compared to our findings. Behbehani et al. have found 95.5% seropositivity among Kuwaitis. A total of 34% of their subjects had titers from 1/128 to 1/4096. They also reported that the age groups from 20 to 31 and from 32 to 43 had the highest number of seropositive persons with medium to high titers, i.e., 1/128 to 1/4096.[13] In our study, the highest rate of seropositivity was found in the age group from 21 to 30 among the male population and from 18 to 20 among the female population. After 40 years of age, the presence of antibodies declined. This finding is consistent with those of Jackson and Hutchinson[12] in the rural blood donors that shows the maximum presence of antibodies in the age group 25 to 44 years. Ahmad et al.[14] have reported acquisition of antibodies early in life in Somalia, in contrast to the findings by Huldt et al.[15] in Sweden, who found that only 8% of children below 10 years were seropositive. In Somalia, it was related to the lower socioeconomic status of the population screened and close association of these people with cats. Feldman and Lamb[16] have reported 10% of the individuals below 20 years and 44% above 30 years of age to have antibodies in the USA. There are no published reports about the prevalence of toxoplasma antibodies among the Saudi children. Our study does not include children, as our subjects were the blood donors who should be between 18 and 50 years of age. The higher rate of seropositivity among 18 to 20-year-old females should be confirmed by further studies as the number of female donors studied is very low (34), and the findings are not comparable to the large number of male donors examined.

The final host of *T. gondii* is the domestic cat. Flies and cockroaches may act as transport hosts. Some nomadic people in Kuwait have been known to be infected with *T. gondii* by eating or handling infected desert rodents and goats.[17]

In Al-Hassa, cats are innumerable, either as pets or strays. The climate is dry and may not favor the survival of oocysts. Probably the transmission of toxoplasma infection in this area is due to ingestion of oocysts or the tissue cysts in the raw or uncooked meat, particularly sheep and goat meat and contaminated vegetables.

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TOPICAL AMPICILLIN FOR PROPHYLAXIS AGAINST WOUND INFECTION IN ACUTE APPENDICITIS

Mohammad Yahya Al-Shehri, FRCSC; Saad Saif, MBBCh; Ahmed Ibrahim, FRCS(Ed);
Saeed Abu-Eshy, FRCS(Glas); Talal Al-Malki, FRCSC; Abdulbasit A. Latif, FRCS;
Tarek Malatani, FRCSC; Abdulaziz Al-Saigh, FRCS(I); Ahmad Al-Nami, MBBCh;
Abdulnasir Batouk, FRCSC

A total of 249 patients, undergoing appendectomy for acute appendicitis, were prospectively randomized into two groups. Group I, comprising 132 patients, received sterile normal saline irrigation to the surgical wound at closure. Alternatively, Group II included 117 patients, who received intraoperative topical ampicillin irrigation of the wound. Both groups were comparable with regard to age, sex, duration of symptoms, and severity of appendicitis. All patients additionally received preoperative systemic gentamicin and Flagyl. Wound infection occurred in 5.3% of Group I compared to only 0.9% of Group II ($P<0.05$). The reduction in infection rate was significant ($P<0.05$) in histologically proven appendicitis. We conclude that the addition of intraoperative topical ampicillin to systemic gentamicin and Flagyl augments prophylaxis against wound infection in acute appendicitis.

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A considerable morbidity following appendectomy is caused by wound infection,[1-5] the rate of which ranges from 9% to 30% in early appendicitis and may reach up to 70% in advanced appendicitis.[3-6] Systemic antibiotics were shown to reduce the wound infection rate significantly.[3,4,7] *In vitro* studies demonstrated 100% kill rates with clinically usable concentrations of antimicrobials in irrigating solutions after only 60-second exposure of the organisms.[8,9] Unlike parenterally administered antimicrobials, topical usage was found to attain prolonged effective local concentrations when used in the powder form.[10]

Experimental studies have shown that the combined use of systemic and topical antibiotics is better in advanced appendicitis than systemic antibiotics alone.[11] Similarly, Seco et al.[12] have concluded in a clinical study that prophylaxis with a combination of systemic clindamycin and topical ampicillin solution, when compared with systemic clindamycin alone, was more effective in preventing wound infection after appendectomy, especially in patients with high wound contamination. However, the study of Seco et al. was criticized because the control group wounds were not irrigated with normal saline and clindamycin may not be the systemic antibiotic of choice for many surgeons. This communication aims at investigating the efficacy of the addition of topical ampicillin to systemic antimicrobials in reducing post appendectomy wound infection rate in a properly controlled randomized prospective study.

Material and Methods

All patients who underwent appendectomy through gridiron incision for clinically suspected acute appendicitis were considered for the study. Exclusion criteria were allergy to ampicillin and other systemic diseases requiring systemic antibiotic administration and therefore three patients who were allergic to ampicillin were excluded from the study, as well as another two patients who had valvular heart disease warranting preoperative prophylactic systemic ampicillin in addition to the systemic gentamicin and Flagyl. A total of 254 patients fulfilled the criteria of the study and were randomized into two groups using sealed envelopes that were opened intraoperatively after the peritoneum was closed. Five patients were withdrawn from the study due to protocol violation. Two patients who were randomized to Group I received their sealed envelopes opened in the beginning of the procedure and were therefore withdrawn because we thought that opening the envelopes before peritoneal closure could be a source of bias. One patient who was randomized to Group II was withdrawn because the appendix was removed through a midline incision. The other two patients were not given topical ampicillin by mistake, despite being randomized to Group II. This left 249 patients who were eligible for the study and further analysis.

Intraoperatively, swabs from the abdominal cavity and from the wound were collected and sent for culture and sensitivity. Both the peritoneal and wound swabs were

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From the Department of Surgery, King Saud University, Abha Branch, College of Medicine, Abha.

Address reprint requests and correspondence to Dr. Al-Shehri: Department of Surgery, King Saud University, Abha Branch, College of Medicine, P.O. Box 641, Abha, Saudi Arabia.

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inoculated and processed as described by Isenberg et al.[13] Antibiotic susceptibility testing was performed using the Bauer and Kirby procedure.[14]

The wounds of 132 patients of Group I were irrigated with 100 ml of sterile normal saline at closure. Alternatively, in Group II, 117 patients had their wounds irrigated with 1 g ampicillin powder dissolved in 100 ml sterile normal saline. All patients received intravenous metronidazole (500 mg for adults and 15 mg/kg/body weight for children) and gentamicin (75 mg for adults and 1.5 mg/kg/body weight for children) one hour before surgery. If the appendix was found to be gangrenous or perforated, antibiotics were continued for five days postoperatively. Development of wound infection or completion of one month without wound infection were considered end points for the study. Wound infection was defined as the presence of purulent discharge in the wound regardless of the culture results or occurrence of serous discharge with a positive growth on culture.[15] Local erythema and/or pain in the absence of discharge or positive culture were not interpreted as wound infection, since it could be due to local hypersensitivity. Bed stay was estimated in both groups so as to calculate the amount of financial savings made by reducing post appendectomy wound infection.

Chi-square "z" test of proportion and Fisher's exact test were used for comparison and the chosen level of significance was 5%. Comparison of the length of hospital stay of patients with and without wound infection was carried out using the Mann-Whitney U-Wilcoxon Rank Sum W Test.

Results

Groups I and II were comparable for age, sex, severity of appendicitis, and duration of symptoms before surgery (Table I). Of those who were withdrawn from the study, the only patient who developed wound infection was one of the two patients who were, by mistake, not given ampicillin, and pathological examination of his appendix revealed that it was acutely inflamed.

Wound infections occurred in 3.2% of the total patients and were equally distributed among the operating surgeons. There were no wound infections in patients with histologically normal appendices.

The median hospital stay in patients who developed wound infection was 5.5 days (range 3 to 11 days), whereas it was only 3.0 days (range 2 to 11 days) in the remaining patients ($P<0.05$).

Seven patients (5.3%) out of 132 developed wound infection in Group I compared to one patient (0.9%) out of 117 patients in Group II (Table 2). The only patient who developed wound infection in Group II was a five-year-old child with gangrenous appendicitis.

Other postoperative complications were infrequent. One patient in each group had some redness in the wound accompanied by pain that subsided spontaneously and was ascribed to the local effect of the adhesive plaster used for dressing. None of the patients developed intra-abdominal or pelvic abscesses. Two patients in Group I and one patient in Group II developed postoperative ileus that resolved on conservative treatment. Three patients in Group II and two patients in Group I developed immediate postoperative fever that was attributed to atelectasis and resolved with chest physiotherapy and early ambulation.

Positive cultures from both the intraoperative abdominal and wound swabs were frequent with advanced appendicitis; less common with acute appendicitis ($P<0.05$) (Table 3). *E. coli* was the most frequent aerobic organism isolated, followed by klebsiella, streptococci, staphylococci, enterococci and pseudomonas species. Almost all streptococci and enterococci were sensitive to ampicillin besides 30% of the *E. coli* isolates.

Wound infection occurred more frequently when the intraoperative cultures were positive. The incidence of wound infection was only 0% to 2% when the intraoperative cultures were negative. With positive intraoperative wound cultures, a significant reduction in

TABLE 1. *Characteristics of the groups.*

	Group I	Group II
Age mean (range)	21 (5-80)	24 (4-66)
Sex (male/female)	90/42	77/40
Normal appendix (total)	27	26
Acute appendicitis (total)	102	88
Advanced appendicitis* (total)	3	3
Duration of symptoms in days		
Mean (range)	1(0.5-4) days	1(0.5-3)
Total	132	117

*=histologically proven gangrenous or perforated appendix.

TABLE 2. *Wound infection rate.*

	Group I	Group II	
Normal appendix	0/27	0/26	ns
Acute appendicitis	6/102 (5.9%)	0/88	$p<0.05$
Advanced appendicitis	1/3 (33.3%)	1/3 (33.3%)	ns
Total	7/132 (5.3%)	1/117 (0.9%)	ns

ns=not significant.

TABLE 3. *Positive intraoperative culture results according to the type of appendicitis.*

Histology	Positive abdominal culture		Positive wound culture	
Normal	7/53	(13%)	4/49	(8%)
Acute appendicitis	42/1	(23%)	34/177	(19%)
Advanced appendicitis	5/6	(83%)	4/6	(67%)
Total	54/242	(22%)	42/232	(18%)

TABLE 4. *Correlation of postoperative wound infection with intraoperative culture results.*

Intraoperative	Group I			Group II				
cultures	Total	Infected	%	Total	Infected	%	Z	P
Abdominal								
+ve	30	5	17	24	1	4	1.452	ns
-ve	99	2	2	89	0	0	1.348	ns
Wound								
+ve	19	5	26	23	0	0	2.621	sig.
-ve	106	2	2	86	1	1	0.402	ns

Sig=significant; ns=not significant.

wound infection occurred in Group II ($P<0.05$) (Table 4). Postoperative cultures from the infected wounds showed *E. coli* in five patients, *Pseudomonas aeruginosa* in addition to *E. coli* in one patient, staphylococcus in one and no growth was found in one patient.

Discussion

Wound infection is still the most common complication following appendectomy and is an important cause of morbidity.[1] The significantly longer hospital stay in our study of the infected group is in agreement with previous studies.[4-7]

Prophylactic use of systemic antibiotics, many of which have been used either alone or in combination, has resulted in a significant reduction in wound infection rate.[2-4] Gentamicin is effective against *E. coli*, which was the most common aerobic organism cultured from the wound and abdomen in our study and this is in agreement with previous studies.[16,17] Unfortunately, culture for anaerobes was not carried out in our study in view of lack of facilities in the emergency setting of our hospital. However, since *Bacteroides fragilis* has been reported to be the most common anaerobic organism in acute appendicitis,[16,17] we believe that systemic Flagyl, which was given routinely in all patients, is an adequate prophylaxis against bacteroides.

A total of 21% (53 patients) of the appendices removed in this study turned out to be normal. This is within the range reported in other places[18] and reflects our attitude of early surgical intervention and is the reason that only six patients with advanced appendicitis were encountered in this study.

Topical antibiotics were found to reduce wound infection following appendectomy.[5-7,11,12,16] Specifically, topical ampicillin was shown to reduce wound infection after colonic,[19] biliary and gastrointestinal surgery[20] and after appendectomy.[21,22] Ampicillin effectiveness is based on its activity against streptococci, enterococci and 30% of the *E. coli* isolates in our study. Its effectiveness against some aerobic and anaerobic bacteria has been also shown by others.[23] Addition of topical antibiotics to systemic antibiotics was found beneficial in advanced appendicitis.[24,25] Bergamini et al.[11] demonstrated in an experimental study that when wound contamination is great, a combination of topical and systemic antibiotics becomes more effective. In this study, we demonstrated that the addition of topical ampicillin to systemic gentamicin and Flagyl also significantly reduces post appendectomy wound infection in early acute appendicitis, which could only be ascribed to the ampicillin effect and not to the mechanical effect of saline irrigation, since a similar benefit was not seen in the control group.

In conclusion, we have demonstrated that the addition of topical ampicillin to systemic gentamicin and Flagyl significantly reduces post appendectomy wound infection rate. This efficacy was well seen in patients with acute appendicitis. In advanced appendicitis, conclusions cannot be drawn due to the small sample size. In our hospital, each bed stay costs approximately SR 1000/day, which is quite remarkable considering the large number of patients undergoing appendectomy. Indeed, hospital bed stay was reduced by 2.5 days/patient by avoidance of wound infection. Our study therefore suggests that the hospital bill can be reduced by routine topical ampicillin application with appendectomy.

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THE GEOGRAPHY OF SICKLE CELL DISEASE: OPPORTUNITIES FOR UNDERSTANDING ITS DIVERSITY

Graham R. Serjeant, MD, FRCP

The sickle cell gene is now known to be widespread, reaching its highest incidence in equatorial Africa, but occurring also in parts of Sicily and Southern Italy, Northern Greece, Southern Turkey, the Middle East, Saudi Arabia, especially the Eastern Province, and much of Central India (Figure 1). This distribution is determined by the occurrence of the sickle cell mutation and its selection by falciparum malaria.

Studies of the structure of DNA surrounding the beta globin locus reveal that the sickle cell gene is associated with several DNA structures probably representing different ancestral populations. The most likely interpretation is that the sickle cell mutation is a relatively recent occurrence that has occurred independently in several different populations. Falciparum malaria then acted as a selective factor, increasing the prevalence of the gene because people inheriting the sickle cell gene from one parent and a gene for normal adult hemoglobin from the other parent (sickle cell trait) were less likely to die from malaria and so more likely to survive and pass on their genes. Over the generations, the sickle cell trait has therefore reached high frequencies in malarious areas. The factor in common to the distribution of the sickle cell gene is therefore malaria and not African ancestry.

The different DNA structures associated with the sickle cell gene are identified by a pattern of restriction enzyme sites, the so-called β globin haplotypes,[1-3] which are assumed to represent independent occurrences of the sickle cell mutation and are named after the places where first described (Figure 2). The Senegal haplotype occurs on the Atlantic coast of West Africa, the Benin haplotype in central West Africa, especially Ghana, Nigeria, and Côte d'Ivoire, and the Bantu or Central African Republic haplotype in Zaire, the Central African Republic, Angola and Kenya.[5] The HbS gene in the Eastern Province of Saudi Arabia[6,7] and in Central India[8] is associated with a different DNA structure not encountered in Africa and so almost certainly a fourth independent occurrence of the sickle cell mutation. It is currently uncertain whether the mutation arose in Arabia and spread to India or vice versa or possibly two independent occurrences in peoples of similar ancestral DNA structures. This fourth pattern is generally called the Asian haplotype.

From these original foci of the HbS mutation, the gene spread along trading routes to North Africa and the Mediterranean, was transported in large populations to

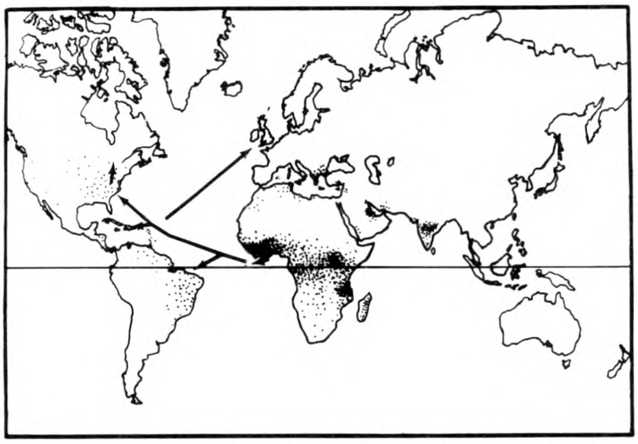

FIGURE 1. Worldwide distribution of the sickle cell gene. Arrows represent major gene flows during the slave trade and latterly emigration.

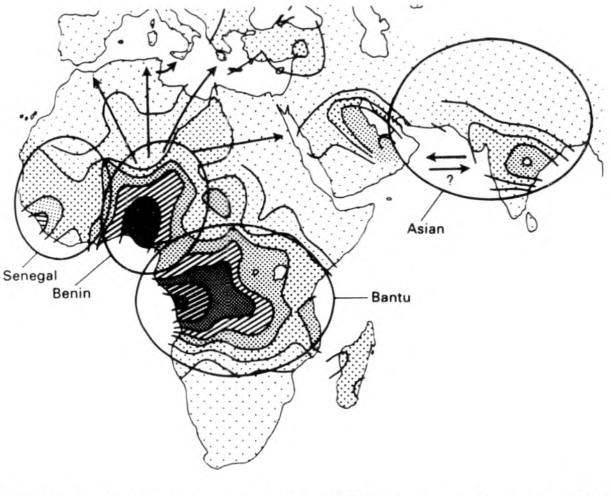

FIGURE 2. Contour map depicting distribution and frequency of the HbS gene upon which is superimposed the distribution of the major β-globin haplotypes (from Ragusa et al[4]).

Address reprint requests and correspondence to Dr. Serjeant: MRC Laboratories (Jamaica), University of the West Indies, Kingston 7, Jamaica, West Indies.

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North and South America and the Caribbean during the slave trade, and latterly has spread to Northern Europe by immigration from the Caribbean, directly from Africa to the United Kingdom, France, Belgium, and Holland, and from Turkey to Germany. The relative prevalence of these haplotypes in the Americas reflects the different origins of their African peoples, approximately 70% of HbS associated chromosomes having the Benin haplotype, 10% Senegal and 10% Bantu. Haplotype frequencies in Jamaica are similar to the USA but the Bantu haplotype accounts for the majority of HbS associated chromosomes in Brazil.[9]

The Benin haplotype accounts for HbS associated chromosomes in Sicily,[4] Northern Greece,[10] Southern Turkey,[11] and South West Saudi Arabia,[6,7] suggesting that these genes had their origin in West Africa. The Asian haplotype is rarely encountered outside its geographic origin because there have been few large population movements and Indian emigrants have been predominantly from non HbS containing populations. However, it is of interest that the Asian haplotype was first described among descendants of Indian indentured laborers in Jamaica.[12] The disease now occurs against diverse genetic and environmental backgrounds, which provide experimental models for investigating the mechanisms of the clinical and hematological variability of the disease.

Genetic Factors

At least four genetic factors contribute to the variability of sickle cell disease; the genotype of the disease, the coincidence of alpha thalassemia or of the genes controlling fetal hemoglobin (HbF) synthesis, and the beta globin haplotype. Other genetic factors contributing to the variability are likely to be recognized in the future.

Genotype of Sickle Cell Disease

Expression of the disease is clearly influenced by the other beta globin genes inherited with HbS.

Homozygous Sickle Cell Disease - inheritance of the gene for HbS from both parents results in homozygous sickle cell disease or SS disease. This is generally the most common condition and the most severe and its prevalence in relation to other forms of sickle cell disease falls with age, reflecting its greater mortality. There is wide clinical variability within SS disease which even in the same environment such as Jamaica may vary from severe complications with death in the first year of life to an extremely mild condition with survival to the late 70s. Factors contributing to this variability include the coincidence of alpha thalassemia or heterocellular persistence of HbF and environmental conditions that are all discussed in later sections.

The pathological basis of the clinical manifestations of sickle cell disease is common to all genotypes but symptoms are generally most frequent and most severe in SS disease. Polymerization of HbS molecules within the red cell raises the internal viscosity and reduces compliance of the cell membrane so that HbS containing cells are less able to negotiate capillary beds leading to premature red cell destruction (hemolysis) and obstruction of blood flow (vaso-occlusion). Most manifestations of the disease are attributed to one or both of these processes. The consequences of rapid hemolysis include anemia, jaundice, pigment gallstones, increased folic acid requirements with a

TABLE 1. *Comparison of some hematological characteristics in four major genotypes of sickle cell disease in Jamaica.*

	SS (n=1295)		$S\beta^0$ thal (n=59)		SC (n=97)		$S\beta^+$ thal type III (n=76)	
	mean (range)	SD	mean (range)	SD	mean (range)	SD	mean (range)	SD
Hb (g/dl)	8.0	1.1	8.9	1.1	11.7	1.7	11.6	1.3
	(4.1-13.5)		(6.6-12.0)		(7.9-16.3)		(9.0-14.7)	
HbA_2 (%)	3.0	0.5	5.0	0.6	-	-	4.7	0.6
	(1.5-4.7)		(3.8-6.6)				(3.5-6.1)	
HbF (%)	6.1	-	7.0	-	1.1	-	5.1	-
	(0.4-33.2)		(0.8-23.8)		(0.3-5.2)		(0.2-20.4)	
MCHC (g/dl)	33.9	1.9	31.8	1.8	34.8	1.2	33.6	1.3
	(27-41)		(28-34)		(32-37)		(31-36)	
RBC (x10^{12}/l)	2.77	0.54	4.03	0.51	4.34	0.71	4.85	0.49
	(1.10-5.48)		(2.95-5.24)		(2.86-5.91)		(3.57-6.26)	
MCV (fl)	87.3	8.1	69.3	5.1	79.3	6.6	73.3	5.2
	(62-115)		(59-84)		(64-95)		(64-85)	
Retics (%)	10.5	-	8.2	-	3.1	-	2.6	-
	(1-31)		(2-17)		(1-8)		(1-7)	

Standard deviations (SD) not given for HbF or reticulocytes where distributions are skewed; HbA_2 levels were not available in SC disease because HbC travels in the same position. Adapted from references 18-21.

tendency to folate deficient megaloblastic change, the aplastic crisis, and the possibility that the greater protein and energy requirements of the accelerated erythropoiesis contribute to the retarded physical and sexual development of the disease. The consequences of vaso-occlusion are determined by the site affected and include stroke, ocular complications, splenic damage with subsequent tendency to acute splenic sequestration and pneumococcal septicemia, acute chest syndrome, leg ulceration, priapism, and possibly renal failure. Both erythropoietic expansion secondary to hemolysis and vaso-occlusion may contribute to the avascular necrosis of bone marrow resulting in dactylitis, painful crisis, avascular necrosis of the femoral head, and other bone damage. In general, the hemolytic aspects of the disease are well tolerated although aplastic crisis and complications of gallstones may occasionally cause death. The painful crisis and leg ulceration are major contributors to morbidity but rarely cause death. The major causes of death are age specific and include acute splenic sequestration, pneumococcal septicemia, and acute chest syndrome in early childhood, acute chest syndrome and stroke in later childhood, acute chest syndrome and pregnancy related problems in early adult life, and chronic pulmonary disease and renal impairment in later adult life.[13]

Sickle Cell-Hemoglobin C Disease - inheritance of the gene for HbS from one parent and the gene for HbC from the other results in sickle cell-hemoglobin C (SC) disease. HbC occurs at high prevalence in Ghana and Burkina Faso[14,15] and is confined to people of West African ancestry, this limited geographical distribution suggesting that the HbC mutation occurred even more recently than HbS. As HbC identifies West African ancestry, SC disease occurs in black populations in North and South America, the Caribbean and Europe but is not seen elsewhere in Africa, around the Mediterranean, Saudi Arabia, or India. SC disease is generally benign with mild symptoms and near normal survival.[16] The only exception to this is proliferative sickle retinopathy (PSR) which occurs more frequently in SC disease than in SS disease,[17] for reasons unknown.

A variety of conditions result from the inheritance of the HbS gene with genes for beta thalassemia and the clinical consequences depend on the type of β thalassemia gene.

Sickle Cell-Beta^0 Thalassemia - Inheritance of the β^0 thalassemia gene (with no production of HbA) from one parent and the HbS gene from the other results in the synthesis of only HbS, HbF, and HbA_2 similar to SS disease. Sickle cell-β^0 thalassemia is therefore a severe condition resembling SS disease electrophoretically, clinically, and hematologically except for a higher HbA_2 and lower red cell indices. Comparison of SS disease and sickle cell-β^0 thalassemia in the Jamaican population shows sickle cell-β^0 thalassemia to have higher total hemoglobin and lower reticulocyte counts (Table 1) consistent with a lower hemolytic rate, persistence of splenomegaly, and less fetal loss,[18] but more painful crises.[22,23]

Sickle Cell-Beta$^+$ Thalassemia - This condition is heterogeneous depending on the type of β^+ thalassemia gene inherited and the amount of normal β chains and hence HbA produced. Many of the different mutations characterize different populations and their geographic site is shown in parentheses after the mutation. Severe β^+ thalassemia genes such as IVS-1 position 5 G→ C (India) and IVS-2 position 745 C→ G (Greece) result in only 3% to 5% HbA and a severe condition indistinguishable from sickle cell-β^0 thalassemia or SS disease (sickle cell-β^+ thalassemia type I). Moderate β^+ thalassemia genes such as IVS-1 position 110 G→ A (Greece) result in 8% to 14% HbA but are also generally severe (sickle cell-β^+ thalassemia type II). Mild β^+ thalassemia genes such as -29 A→ G, -88 C→ T (West Africa), or IVS-1 position 6 T→ C (Greece) result in 18% to 25% HbA and a generally mild clinical course (sickle cell-β^+ thalassemia type III).

The distribution of the genotypes of sickle cell disease depends on the geography of the individual genes. SS disease occurs in all peoples manifesting HbS. SC disease is confined to populations of West African ancestry. Sickle cell-β^0 thalassemia occurs in all populations and accounts for nearly half the sickle cell disease observed in Greece.[24] Sickle cell-β^+ thalassemia is always mild (type III) in African populations but is generally severe (types I or II) in Greece and India, and appears rare or non-existent in Saudi Arabia. Among populations of West African ancestry observed in Jamaica, there are four principle genotypes of the disease, SS disease, SC disease, $S\beta^+$ thalassemia type III, and $S\beta^0$ thalassemia. They may be distinguished by alkaline hemoglobin electrophoresis (Figure 3) although differentiation of SS disease and $S\beta^0$ thalassemia may require family studies, red cell characteristics, and HbA_2 quantitation. There are marked hematological (Table

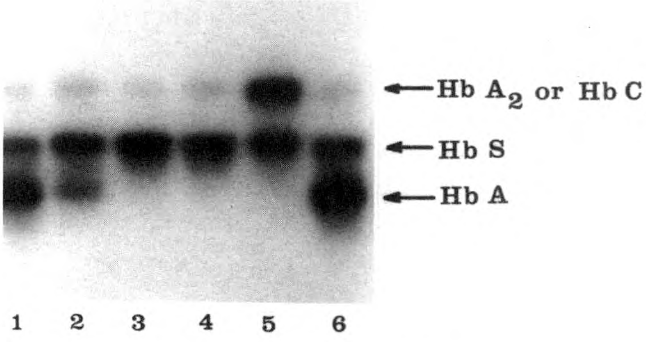

FIGURE 3. Starch gel electrophoresis of the four most common genotypes of sickle cell disease: 1) AS control; 2) Sβ+ thalassemia type III; 3) SS disease; 4) $S\beta^0$ thalassemia; 5) SC disease; and 6) AS control (photo courtesy of Dr. Paul Milner).

TABLE 2. *Comparison of some clinical characteristics in four major genotypes of sickle cell disease in Jamaica.*

	SS	$S\beta^0$ thal	SC	$S\beta^+$ thal
Painful crisis	++	+++	+	+
Acute chest syndrome	++	++	+	+
Leg ulceration	++	+	±	±
Cardiomegaly	+++	++	+	±
Systolic murmurs	++	++	±	±
Jaundice	0–+++	+	±	0
Splenomegaly	Age dependent	++	++	++
PSR	±	±	++	++
ANFH	+	+	±	±
Bone marrow expansion	++	++	+	±
Priapism	++	+	±	0
Retarded physical development	++	+	±	0
Abnormal habitus	++	++	0	0
Increased fetal loss	+	±	0	0

PSR=proliferative sickle retinopathy. ANFH - avascular necrosis of femoral head. 0—+++ representing increasing severity or frequency of complications. Data derived from references 16-18,21.

1) and clinical (Table 2) differences between these genotypes.

Alpha Thalassemia

Most populations have four alpha globin genes, a pair of tightly linked alpha globin genes (αα/αα) on each chromosome 16. Deletion of one of a pair of these genes resulted in the mild alpha$^+$ thalassemia (α-) which may be inherited from one (α–/αα) or both parents (α–/α–). Deletion of both genes on a chromosome results in the severe alpha^0 thalassemia gene (- -) which may also be inherited heterozygously (- -/αα) or homozygously (- -/- -). In some populations, alpha$^+$ and alpha^0 thalassemia may occur, giving rise to the double heterozygote (α–/– –) manifested by HbH disease. In practice, the severe alpha^0 thalassemia gene occurs predominantly in South East Asia and so rarely, if ever, coincides with HbS. The mild alpha$^+$ thalassemia, on the other hand, is extremely common in populations with HbS, the heterozygous form occurring in approximately 35% and the homozygous form in 3% to 4% of populations of West African ancestry in the USA.[25] In the Eastern Province and in the South West of Saudi Arabia[6,7] and in India,[26,27] this form of alpha thalassemia occurs in over 50% of populations with sickle cell disease. The only population in which sickle cell disease does not coincide with frequent alpha thalassemia is Greece.[28] In Saudi Arabia, deletional alpha thalassemia is common but nondeletional forms may also occur and coincide with SS disease.

The alpha globin genes are on a different chromosome from the beta globin genes and alpha thalassemia may be inherited with any form of sickle cell disease. The co-inheritance of alpha thalassemia modifies the hematological and clinical expression and this interaction has been best documented in SS disease.[29,30] Hematologically, alpha thalassemia increases total hemoglobin and HbA_2 and reduces the hemolytic rate, mean cell hemoglobin concentration (MCHC), mean cell volume (MCV), reticulocyte count, bilirubin level, and counts of irreversibly sickled cells, these effects being more marked with homozygous alpha thalassemia than in heterozygotes (Table 3). Clinically, there is less leg ulceration and acute chest syndrome; splenomegaly persists because this capillary bed has not been destroyed by sickling and therefore represents a manifestation of mildness, but there is a greater risk of painful crises (Table 4).

TABLE 3. *Comparison of some hematological characteristics in four major genotypes of sickle cell disease in Jamaica.*

	Normal controls (αα/αα) n=88		Heterozygous α^+ thalassemia (α–/αα) n=44		Homozygous α^+ thalassemia (α–/α–) n=44	
	mean (range)	SD	mean (range)	SD	mean (range)	SD
+Hb (g/dl)	7.8	1.1	8.1	1.0	8.8	1.3
	(6.0-10.5)		(5.8-10.8)		(6.9-11.5)	
*HbA_2 (%)	2.8	0.4	3.1	0.3	3.9	0.4
	(2.1-3.8)		(2.4-3.9)		(3.0-4.7)	
§HbF (%)	5.3	-	4.8	-	3.8	-
	(0.6-18.0)		(0.9-15.0)		(0.8-18.4)	
*MCHC g/dl)	34.8	1.7	34.3	1.6	32.8	1.3
	(31-39)		(30-39)		(30-36)	
*RBC (x10^{12}/l)	2.56	0.39	2.90	0.47	3.86	0.59
	(1.80-3.70)		(2.10-4.50)		(2.80-5.00)	
*MCV (fl)	90.1	6.1	84.4	7.8	71.2	3.2
	(69-101)		(63-96)		(63-78)	
*Retics (%)	11.9	-	9.3	-	6.4	-
	(5-25)		(4-17)		(3-12)	

*=significant differences bewteen all groups; +=significant differences between α–/αα and α–/α– and between αα/αα and α–/α– ; §=significant difference only between αα/αα and α–/α– ; Adapted from Higgs et al[30]

TABLE 4. *Comparison of some clinical features in SS disease with and without alpha thalassemia.*

	Normal controls (αα/αα)	Heterozygous α^+ thalassemia (α–/αα)	Homozygous α^+ thalassemia (α–/α–)
Painful crisis frequency	+	+	++
*Acute chest syndrome (% affected)	34%	30%	16%
*Leg ulceration	45%	36%	23%
*Splenomegaly	14%	24%	45%
Avascular necrosis of femoral head	+	?	++

*=risks were significantly different between αα/αα and α–/α– groups. Data derived from references 22,23,29-33.

Inheritance of High Fetal Hemoglobin Levels

Levels of HbF vary markedly in patients with SS disease and some patients maintain high levels of gamma chain synthesis into adult life. HbF molecules interfere with polymerization of HbS molecules and hence inhibit sickling, and patients with high HbF levels are protected from many of the early life-threatening complications of the disease.[34,35] High levels of HbF are associated with a more mild clinical course, more normal growth, persistence of splenomegaly, less leg ulceration and acute chest syndrome, less end organ damage, and probably greater survival. Hematologically, the associations with high HbF levels are complex but high HbF levels generally result in a higher total hemoglobin.[36]

The inheritance of genes determining high levels of HbF is not well understood. In most SS subjects with high HbF levels, either one or both parents show a modest elevation of HbF within the normal range. However, since HbF levels decline with age and are higher in females than in males, it has not been possible to define the gene on the basis of a set HbF level. On current evidence, it seems likely that HbF levels in SS disease are determined by several factors, some environmental and some genetic. Since HbF protects against sickling, red cells with high HbF levels persist for longer in the circulation, tending to elevate hemolysate HbF levels because of cell selection.[37] Possible genetic factors that may contribute to the elevation of HbF levels include a gene well separated from the beta globin locus possibly on a different autosome,[38] the X chromosome,[39] and the Asian haplotype.[40,41]

Beta Globin Haplotypes

The four independent occurrences of the HbS mutation provide a useful experimental model since varying disease expressions in the different haplotypes may be attributable to differences in DNA structure surrounding the β globin gene. Studies of the clinical and hematological expression of the different haplotypes have been limited by the relatively small numbers with Senegal and Bantu haplotypes in the studied populations and by ascertainment biases. There is some evidence that HbF levels are higher in patients with the Senegal haplotype[42] although it is unclear whether this requires heterozygosity or homozygosity for the haplotype. HbF levels seem lower in the Bantu haplotype[43] and are highly variable in the Benin haplotype. High HbF levels are usually associated with the Asian haplotype in SS disease and even in Indian AS subjects, the HbF level increased with the number of copies of this haplotype.[44] However, in the Eastern Province of Saudi Arabia where the population is homogeneous and virtually all homozygous for the Asian haplotype, (although the mean HbF level is high), there is still marked variability in HbF levels.[7] The influence of haplotype on HbF levels is therefore unclear at the present time and even greater uncertainty attends the possible effects of haplotype on clinical course.

Environmental Factors

The sickle cell mutation and sickle cell disease initially emerged in a tropical climate with many adverse environmental factors including malaria, other infections, infestations, and malnutrition. It has since spread to a variety of more temperate climates, to environments where malaria no longer occurs, and infections and malnutrition have been controlled. The changing surroundings have also been associated with differences in disease expression that contribute to an understanding of the causes of different manifestations of the disease.

Infections

The control of malaria is a major factor in improving morbidity and mortality of sickle cell disease. Although subjects with the sickle cell trait have a relative resistance to malaria, patients with sickle cell disease do not, and malaria is a common precipitating factor for painful crises[45] and by causing an additional severe hemolytic anemia, a major contributor to death.[46] Other common childhood infections are likely to carry a higher morbidity when superimposed on sickle cell disease and their prevention by effective and complete immunization programs also improves outcome of the disease. The morbidity and mortality from pneumococcal septicemia may now be reduced or prevented by prophylactic penicillin in early childhood and pneumococcal vaccine at later ages.[47,48] Salmonella septicemia and osteomyelitis are potentially life threatening complications, the incidence of which reflect the frequency of Salmonella carriage in the general population and are consequently likely to be reduced by properly treated piped water supplies and correct sewage disposal.[46,49] The aplastic crisis from human parvovirus infection is yet another infectious complication[50] where proper monitoring and intervention may reduce mortality. Regimes for control of many of these infections are available and whether they are effectively implemented depends upon the development of health care services in the individual countries. The relative sophistication of health care services in North America, the Caribbean, and Europe implies that patients should be protected from such infections and consequently have less morbidity and greater survival.

Nutrition

Balanced nutrition is also important since the rapid hemolytic rate increases energy requirements and demands for specific nutrients, especially in SS disease. The additional requirements for folic acid must be balanced by increased dietary availability or by supplementation in order to avoid the marked anemia resulting from megaloblastic erythropoiesis. This is particularly important in West Africa[51] where dietary availability appears to be low and megaloblastic change common. In North America, the Caribbean, and Europe folate deficiency appears less common, even in the absence of supplementation, and probably reflects the lesser demands in the absence of malaria.

Climate

Climatic change may also be important. Cold wet weather is recognized to be an important precipitating factor for the painful crisis in West Africa[52] and this relationship is also apparent in the Caribbean[53] and North America. Theoretically, exposure of patients to more extreme conditions should be followed by more frequent pains although this relationship may be obscured by modification of the micro-climate with warm clothing and central heating. On the other hand, a hot dry climate such as Saudi Arabia may predispose to dehydration as a risk factor for painful crises. The painful crisis is a major determinant of morbidity among adolescents and young adults but although death may occur, the painful crisis is infrequent as a direct cause of mortality. However, the exposure to transfusion and to potentially addictive analgesics in the treatment of painful crises may have serious implications for some patients.

Medical Care

The provision of specialized medical services for patients in Sickle Cell Clinics is likely to alter the morbidity and outcome of the disease. Such clinics act as centers for education about the disease for both patients and their families. An example of the impact of parental education in reducing mortality from the disease is provided by experience with acute splenic sequestration.[54] The etiology of this complication is unknown but sudden enlargement of the spleen traps red cells, resulting in a sudden severe anemia and often death. Treatment consists of early diagnosis and prompt blood transfusion and, if the complication recurs, prophylactic splenectomy. However, a high mortality attends the first episode and parental education informing the mother of this complication, how to diagnose it, and what to do, was shown to reduce the mortality by approximately 90% in Jamaica.

Sophisticated facilities may ironically increase morbidity and possibly mortality if incorrectly used. Patients may be subjected to exploratory surgery which would have been avoided with greater experience of the disease. Episodes of deep jaundice attributable to acute cholestasis may be subjected to exploratory surgery to exclude obstruction of the common bile duct and laparotomy may be performed in the painful abdominal crisis rather than conservative management. The frequent dependence on blood transfusion in the management of pregnancy and of certain acute complications may be deleterious, resulting in iron accumulation, transfusion borne infections, or alloimmunization which may actually contribute to the death of the patient.

Age and Secular Changes

Prognosis and survival in sickle cell disease are also influenced by the age of the patient. In SS disease, the greatest mortality occurs in the second six months of life and mortality declines for each individual subsequent year. This implies that the prognosis for a 10-year-old patient is better than that for a newborn who has yet to traverse the early high risk period. Furthermore, the morbidity may also improve with advancing age, the susceptibility to infection appearing to wane and painful crises becoming less frequent and less severe in most patients after the age of 30 years.

Interpretation of these age effects may be further confounded by secular changes, since improving management of the disease will certainly improve survival and a 10-year-old patient today must have a better prognosis than a similar subject 20 years ago.

Geographic Variation of Sickle Cell Disease

The interaction of these various genetic and environmental influences determines the clinical pattern of sickle cell disease in its different locations.

West Africa

The sickle trait frequency varies from 15% to 25% and the HbC trait frequency from 3% to 4% in Nigeria to 15% to 20% in parts of Ghana and Burkina Faso, so the predominant genotypes of sickle cell disease are SS and SC disease, the latter being proportionately more frequent in Ghana. Data on $S\beta^+$ thalassemia and $S\beta^o$ thalassemia are insufficient to predict their relative prevalences. Alpha$^+$ thalassemia is common. Malaria is common and general public health measures poor outside major cities. High socioeconomic status improves survival,[55] ensuring easier access to medical care, better public health measures, better immunization and nutrition, and better malarial prophylaxis. Few figures are available but mortality is high and survival to adult life uncommon. Most mortality is attributable to malaria or other infections. Leg ulceration and other end organ damage such as renal failure are uncommon, presumably because patients do not survive long enough to develop these complications. Pregnancy is also infrequent and pregnancy related pathology consequently rare in SS disease although more common in SC disease.

Jamaica

The population is predominantly of West African origin but malaria has been eradicated and public health measures are generally well developed. There are four major genotypes of sickle cell disease: SS disease occurring in every 300 births, SC disease in every 500 births, $S\beta^+$ thalassemia type III in every 3000 births and $S\beta^o$ thalassemia in every 7000 births.[56] Alpha$^+$ thalassemia occurs heterozygously in 35% and homozygously in 3.5%.

In SS disease, there is an 85% survival to 10 years, probably over 50% survive to 30 to 40 years and some patients survive to their late 70s. The greatest mortality is in the first year of life, falling for each succeeding year, but rising again in early adult life. Splenomegaly persists in approximately 10% of SS patients beyond the age of 15 years. Leg ulceration that occurs in up to 75% of SS patients and stuttering priapism which is reported in approximately 40% of postpubertal males are particularly characteristic of the disease in Jamaica.

North America

The reported disease from North America is similar to that described in Jamaica except for a much lower prevalence of leg ulceration at 5%.

Europe

No studies are available on the natural history of sickle cell disease in Europe but observations in the United Kingdom and France suggest that the disease does not differ from that observed in Jamaica except for a lower prevalence of leg ulceration.

Greece

The relative prevalences of the different genotypes of sickle cell disease in Greece differ from that in West African populations because of high frequency and variety of β thalassemia genes. The HbS gene occurs at high prevalence in some Northern Greek villages, especially in the Halkidhiki peninsula and β^0 thalassemia genes are common in the South. Admixtures of the population result in a sickle cell clinic at Thessaloniki in Northern Greece serving approximately equal numbers of SS disease and $S\beta^0$ thalassemia and three types of $S\beta^+$ thalassemia (types I, II, and III) of which type II predominates.[23]

Comparing Greek and Jamaican SS disease, Greek subjects had higher hemoglobin levels and red cell counts and lower MCHC and reticulocyte counts.[28] The higher hemoglobin and lower reticulocyte counts are consistent with less hemolysis, but Greek subjects have neither of the genetic factors recognized to ameliorate hemolysis in patients of African origin, alpha thalassemia or high levels of HbF. Clinically, Greek SS subjects show persistence of splenomegaly, more normal body build, and less leg ulceration and priapism.

Saudi Arabia

The genotypes of sickle cell disease are predominantly SS disease and $S\beta^0$ thalassemia. Deletional alpha thalassemia occurs in over 50% of the population and non-deletional forms also occur. There are two different forms of SS disease, the South West manifesting the Benin haplotype and presumably imported from Africa, and the Eastern Province having the Asian haplotype and probably representing an independent occurrence of the sickle cell mutation. Saudi Arabia therefore offers an opportunity to compare the effects of the two haplotypes within a similar environment.

Compared to South Western patients, Eastern patients have higher hemoglobin and HbF, and lower HbA_2, MCV, reticulocyte and platelet counts. Clinically, Eastern patients had less dactylitis, later onset of painful crises, persistent splenomegaly, less acute chest syndrome, and thicker skin folds.[7] Leg ulceration and priapism were rare in both groups.

India

The common genotypes in a study in Orissa[19] were SS disease and $S\beta^+$ thalassemia type I resulting from a mutation at IVS-1 position 5 G→ C. Deletional α^+ thalassemia occurred in over 50% of the group, and almost all had the Asian haplotype. Compared to Jamaican patients, Indian patients with SS disease had higher hemoglobin, red cell counts and HbF levels and lower HbA_2, MCHC, MCV, and reticulocyte counts. Clinically, splenomegaly persisted for longer, and leg ulceration and priapism were rare. SS disease in Orissa was therefore very similar to that in the Eastern Province of Saudi Arabia.

Comparison of Four SS Patient Groups

The results of these differing genetic and environmental backgrounds are illustrated by comparisons of SS disease in four different areas - Jamaica, Greece, Eastern Saudi Arabia, and Central India. A summary of molecular genetic features (Table 5) shows alpha^+ thalassemia to be rare in Greece, common in Jamaica, and even more common in Saudi Arabia and India. Beta globin haplotypes are predominantly Benin in Jamaica, entirely Benin in Greece and almost entirely Asian in the other two groups. The resulting hematological differences (Table 6) are largely but not entirely attributable to these genetic differences and the clinical differences (Table 7) in large part reflect the hematological differences. Some clinical features such as the high prevalence of leg ulceration in Jamaica or of Salmonella osteomyelitis in Saudi Arabia are presumed to result from environmental factors and others such as the high prevalence of avascular necrosis of the femoral head in Saudi Arabia may be exaggerated by symptomatic selection in the studied population.

Comparable and reliable incidence data for painful crises in the four populations are not available, but painful

TABLE 5. *Alpha thalassemia and beta globin haplotype in homozygous sickle cell disease in four geographic areas.*

	Jamaica	Greece	Eastern Saudi Arabia	Orissa State India
Alpha thalassemia (α-gene) frequency	0.185	0.037	0.375	0.317
Beta globin haplotype	60% Benin	Benin	Asian	Asian

Data from references 10, 19, 28.

TABLE 6. *Comparison of some hematological indices in homozygous sickle cell in four geographic areas depicted as mean (range).*

	Jamaica	Greece	Eastern Saudi Arabia	Orissa State India
HbA_2	2.96 (1.5-4.7	2.82 (1.9-4.0)	2.18 (1.2-4.0)	1.89 (1.1-3.4)
Corrected HbA_2 (%)	3.15 (1.8-4.8)	2.98 (2.1-4.0)	2.52 (1.4-4.7)	2.25 (1.4-3.7)
HbF (%)	6.11 (0.4-33.2)	5.58 (0.7-13.6)	13.34 (4.9-22.1)	16.64 (4.5-31.5)
Hb (g/dl)	8.04 (4.1-13.5)	9.36 (5.7-11.9)	10.27 (6.5-12.9)	8.73 (3.9-13.5)
MCHC (g/dl)	33.9 (27-41)	32.8 (30-38)	32.9 (27-39)	31.5 (25-42)
MCV (fl)	87.3 (62-115)	92.8 (68-108)	82.4 (52-105)	83.6 (63-113)
Retics	10.5 (1-31)	7.9 (2-16)	5.9 (2-14)	6.5 (1-29)

Data from references 10, 19, 28.

TABLE 7. *Some clinical features of homozygous sickle cell disease in four geographic areas.*

	Jamaica	Greece	Eastern Saudi Arabia	Orissa State India
Painful crisis	++	++	++	++
ANFH	8%	12%	27%	?10%
Leg ulceration	75%	2%	0%	1%
Priapism (% males)	40%	8%	6%	0%
Splenomegaly	5%	19%	53%	69%

Data from references 10, 19, 28.

crises remain a major source of morbidity even in Eastern Saudi Arabia and India despite the high HbF levels characterizing these groups. The high frequency of alpha$^+$ thalassemia would be expected to increase the risk[22,23] and high HbF levels decrease the risk[23] of painful crises. However, a high hemoglobin is a risk factor for painful crises,[23,57] and since painful crises continue as an important manifestation of the disease in these populations, one must conclude that the high hemoglobin consequent on alpha$^+$ thalassemia has more than offset any protective effect from high HbF levels. Contrary to the common assumption that high hemoglobin levels imply mild disease, a high hemoglobin may also be a risk factor for avascular necrosis of the femoral head,[58] proliferative sickle retinopathy,[59] and acute chest syndrome (Castro-personal communication). The mechanism of high hemoglobin levels determines their clinical significance, high hemoglobin associated with high HbF levels being relatively benign[36] but alpha thalassemia leading to high hemoglobin with low HbF levels being potentially deleterious.

The low prevalence of leg ulceration in Saudi Arabia and India is consistent with a protective effect of alpha$^+$ thalassemia or high HbF levels as supported by data from Jamaica and the USA.[30,60] However, leg ulceration remains extremely common in Jamaica despite a high prevalence of alpha$^+$ thalassemia, and the assumption that poor socioeconomic conditions were responsible was not supported by data from India where such conditions are common but leg ulceration rare. One must conclude that some other factor, not yet recognized in Jamaican conditions, is responsible.

The infrequency of priapism in Saudi Arabia and India is consistent with their high HbF levels and observations that low HbF levels are a risk factor for this complication in Jamaica.[61]

The data on avascular necrosis of the femoral head are difficult to interpret and subject to symptomatic selection in the study groups, although it seems unlikely that this could account entirely for the high prevalence observed in Saudi Arabia.[7] Alpha$^+$ thalassemia is a risk factor[31-33] from studies in the USA but did not account for the high prevalence in Saudi Arabia (Padmos and Serjeant - unpublished observations) which currently remains unexplained.

High levels of HbF and alpha$^+$ thalassemia are associated with persistence of splenomegaly,[30,62] implying persistence of splenic function.[63,64] Subjects in Eastern Saudi Arabia and India should therefore be protected from pneumococcal septicemia and acute splenic sequestration[34,54] but may be at greater risk of hypersplenism.[19,65]

The ultimate significance of these differences lies in their effect on mortality and although little data are available, it would be anticipated that SS patients in Eastern Saudi Arabia and India would be relatively protected from the serious early complications of acute splenic sequestration and pneumococcal septicemia. The greater red cell survival in alpha$^+$ thalassemia[66] and high HbF levels should decrease mortality from the aplastic crisis. Data on the incidence of stroke in Eastern Saudi Arabia and India are not available but might be predicted to be less common. Finally, the progressive end organ damage resulting in chronic pulmonary fibrosis[67] and renal impairment[68] that are major determinants of mortality in SS adults from Jamaica and the USA do not appear to be common in Eastern Saudi Arabia or India. These observations are consistent with the low mortality reported from Eastern Saudi Arabia in both children[69] and adults[70] and the calculations of near normal survival[71] in that area.

In conclusion, the manifestations of sickle cell disease are influenced by a variety of other genetic and environmental factors. The occurrence of the disease against different genetic and environmental backgrounds provides experimental models that contribute to understanding the variability in clinical and hematological expression of the disease. Improvement in environmental conditions will decrease both the morbidity and mortality associated with the disease. The Asian haplotype of the disease as manifested in Eastern Saudi Arabia and India has many benign features but still causes significant pathology.

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Case Reports

CRYPTOCOCCAL MENINGITIS: REPORT OF A CASE

George F. Araj, PhD, ABMM; Umaya M. Musharafieh, MD;
Rima A. Mughnieh, MD; Marwan M. Uwaydah, MD

Cryptococcus neoformans is a saprophytic encapsulated yeast with a worldwide distribution in soil contaminated usually with avian excreta, mostly from pigeons.[1] Infection is acquired by inhalation of the organism and could be asymptomatic and limited to the lungs, especially in the immunocompetent host.[2] Hematogenous dissemination, especially to the meninges, and fatal outcome occur in patients with impaired cell-mediated immunity secondary to a variety of conditions, particularly malignancy, diabetes mellitus, treatment with corticosteroids, and infection with the human immunodeficiency virus (HIV).[3,4]

Despite the marked increase in the number of immunocompromised patients and the parallel increase in the incidence of cryptococcosis around the world, reports concerning this infection from our region are scarce.[5] Herein we describe the first case report of *C. neoformans* meningitis from Lebanon and present an update on the pertinent literature, especially in relation to non-AIDS versus AIDS patients.

Case Report

A 46-year-old female with myasthenia gravis diagnosed in 1988 has been maintained on prednisone (60 mg/day) and physostigmine (60 mg q.6h.). On 21 February 1992, the patient presented to the emergency unit of the American University of Beirut Medical Center (AUBMC) with a 10-day-history of fever, headache, vomiting, productive cough, mental changes, and ampicillin intake for one week. Examination revealed a temperature of 39°C, pulse rate 85/min, respiratory rate 20/min, BP 160/85 mm/Hg. The physical examination was unremarkable except for cushingoid facies and tender abdomen. Neurologic examination revealed the patient to be disoriented to time, place and person, responsive to verbal orders, with positive Kernig and Brudzinski signs.

Computed tomogram (CT) scan of the brain showed a moderate degree of dilatation of the ventricular system. Chest x-ray was normal. The hemogram, renal, and liver function tests as well as electrolyte studies were within normal limits except for elevated blood sugar (16 mmol/L) and white blood count (WBC) of 16×10^9/L (71% PMN, 29% lymphocytes). ELISA test for HIV 1 and 2 and the PPD test were negative. Urinalysis showed abnormality in pH (9) and sugar (4+). Blood and urine cultures were negative. Cerebrospinal fluid (CSF) studies were done on presentation and subsequently are shown in the table. The patient was admitted as a case of partially treated meningitis and started on a combined therapy of ceftriaxone and penicillin G. Her blood sugar was stabilized and the prednisone tapered to 20 mg/day.

On 19 March 1992, the india ink examination of the CSF revealed encapsulated budding yeast cells. Immediately, the antibiotics were discontinued and amphotericin-B was started. Five days later, 5-flucytosine was added. The CSF culture grew *C. neoformans*. Repeat lumbar punctures (LP) were performed to relieve CSF pressure and for investigative purposes (Table).

On 8 April 1992, the patient developed pneumonia due to methicillin-resistant *Staphylococcus aureus* which was controlled by vancomycin. Meanwhile, adverse effects to the antifungal agents began to appear. The amphotericin-B dose was decreased from 60 mg to 30 mg/day.

TABLE : *CSF findings at different intervals during hospitalization.*

	Dates of findings			
Investigation	21 February 1992G	19 March 1992G	12 April 1992G	30 April 1992G
Gram-stain	NS	Y(±)	NS	NS
Acid-fast stain	NS	NS	ND	ND
India ink	NS	EY(++)	NS	NS
WBC				
Total ($\times 10^9$/L)	660	183	21	6
PMN (%)	45	9	3	0
Lymphocytes (%)	55	91	97	100
Glucose (mmol/L)	3.2	1	5.4	1.9
Protein (mg/L)	174	200	86	54
Culture	NG	Cm	NG	NG

CSF=cerebrospinal fluid; Cm=*Cryptococcus neoformans*; ND=not done; NG=no growth; NS=none seen; EY=encapsulated yeast cells; Y=yeast cells; ±=few; ++=many; WBC=white blood cell (count); PMN=polymorphonuclear leukocyte.

From the Departments of Laboratory Medicine (Dr. Araj) and Medicine (Drs. Musharafieh, Mughnieh, Uwaydah), American University of Beirut Medical Center, Beirut.

Address reprint requests and correspondence to Dr. Araj: Department of Laboratory Medicine, American University of Beirut Medical Center, P.O. Box 113-6044, Beirut, Lebanon.

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On 29 April 1992, the patient had generalized seizures with decrease in the level of consciousness. Epanutin was started and diazepam was administered as needed. Repeat metabolic profile and sepsis workup were nonrevealing. CT of the brain showed severe hydrocephalus as compared to initial CT. A VP shunt was inserted without complications. However, on 23 May 1992, the patient became tachypneic and dyspneic with respiratory distress. Arterial blood gases revealed PO_2 of 40, PCO_2 of 55 and pH of 7.21. She was immediately intubated. Eight hours later the patient sustained cardiopulmonary arrest and expired.

Discussion

Reaching a definitive diagnosis in patients with cryptococcal meningitis could be delayed, as the clinical presentation and routine hematologic, biochemical, and CSF results may overlap with a variety of noninfectious and infectious diseases, especially those endemic in our area, tuberculosis and brucellosis,[6,7] making the differential diagnosis perplexing to the unaware. In fact, the initial diagnosis of this case was considered as partially treated bacterial meningitis. However, in view of the medical history and steroid therapy, the possibility of chronic meningitis was pursued.

With the increase in the number of AIDS cases, interest in studying the clinical features of cryptococcal meningitis in these patients evolved, especially to compare them with those described in the pre-AIDS era.[2,8] Differences in the incidence of some signs and symptoms were noted between non-AIDS and AIDS patients: headache (87% vs 81%), fever (60% vs 88%), mental status changes (52% vs 19%), meningeal signs (50% vs 31%), photophobia (33% vs 19%), and seizures (15% vs 8%). Since 10% of non-AIDS or AIDS patients were asymptomatic, it is recommended that the CSF be examined in any patient with extraneural cryptococcosis.[8] Moreover, the skull and chest x-ray examinations also fail to provide a definitive diagnosis, as they may not show abnormality, or if abnormality is present (usually in less than half of the patients), it is not characteristic of the disease.[9] However, the cephalic CT is recommended in suspected cases with cryptococcal meningitis to ascertain the presence of mass lesions, granulomas, edema or hydrocephalus, especially since the CNS involvement can present in various ways: subacute or chronic meningitis, encephalitis, focal brain or spinal cord lesions.[2,9]

The routine examination of CSF usually suggests a chronic lymphocytic meningitis. Generally, the CSF findings in non-AIDS patients are similar to those in AIDS patients.[2] However, low CSF WBC ($<20\times10^9$/L) is strikingly more noted in AIDS than in non-AIDS patients (69% vs 30%) with cryptococcal meningitis.[4,10] In addition, culture-proven cryptococcal meningitis could occur in the presence of normal initial CSF findings in immunocompromised patients.[11] Because of these limitations on routine CSF examinations, specific tests should be relied upon in confirming the suspected diagnosis. These include india ink smear, culture and antigen detection that show positivity in 60%, 75%, and 95% respectively in initial CSF examination.[2,12,13]

Mortality in untreated cryptococcal meningitis reaches 86% as compared to 20% to 25% in patients treated with antifungal agents.[8] A six-week course of amphotericin-B has been the regimen of choice since 1951.[14-16] Although the combination of amphotericin-B and 5-FC has also been used, so far there is no conclusive evidence to show its superiority over using amphotericin-B alone.[2,16] In patients with AIDS, the use of 5-FC is not advisable due to possible exacerbation of bone marrow suppression. In addition, maintenance therapy with a single weekly dose of amphotericin-B (80 mg to 100 mg IV) is needed in these patients to avoid relapse.[10]

Despite the high toxicity of the currently used drugs, none of the tried alternatives including ketoconazole,[17] itraconazole,[18] and fluconazole[19] have been recommended for the initial treatment of cryptococcal meningitis at this stage. However, both itraconazole and fluconazole seem promising in therapy failure and maintenance therapy of AIDS patients with cryptococcal meningitis.[20,21]

In addition to antifungal therapy, surgery can be a helpful adjunct in the treatment of cases with intracerebral lesions or those with combined pulmonary and neural cryptococcosis.[5] Despite the 75% to 80% cure rate in treated patients, 40% to 50% of the cured suffer neurological sequelae including visual loss, cranial nerve palsy, significant motor dysfunction or impairment of mental status.[12,22]

The prognosis of cryptococcal meningitis is variable and depends on several factors.[23] Favorable outcome was observed with decreasing antigen titers in CSF and serum specimens. Unfavorable outcome has been associated with CSF elevated opening pressure, positive india ink, low WBC ($<20\times10^9$/L), no decrease in CSF or serum antigen during therapy, positive extraneural cultures, daily dose of >20 mg prednisone and patients with organ transplants or AIDS.[8] Despite the absence of dissemination, the present patient falls within the poor outcome category because of her diabetes mellitus, corticosteroid therapy, and progressive hydrocephalus.

In conclusion, although cryptococcal infection has been rarely reported from our region, all the factors for its existence are available in this part of the world. Thus, the differential diagnosis of cryptococcal meningitis should be pursued when investigating febrile immunocompromised patients with signs and symptoms involving the central nervous system.

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CAVERNOUS HEMANGIOMA OF THE PAROTID GLAND

Jamal T. Hamdi, FRCSEd; Mohan Kameswaran, FRCS;
Saeed Abu-Eshy, FRCS; Tarek Malatani, FRCSC

Hemangioma is perhaps the most common tumor of the major salivary glands during infancy and childhood.[1-5] Krolls et al.[6] found it to occur second to pleomorphic adenoma in infancy. It accounts for 1% to 5% of all salivary gland tumors, and over 90% are found in the parotid gland.[7-9] There is a controversy over whether or not hemangioma is a true benign tumor of blood vessels[10] or a vascular malformation, i.e., a hamartoma.[11-13] Caldwell and Campbell[14,15] reported the first parotid hemangioma in the British literature while Faber et al.[12] reported the third series of adult parotid hemangioma in the British literature in 1978 after Gascoyen,[16] Dempsey and Murley.[11] Nomenclature of the tumor varies from author to author; Peel and Gnepp[17] present the most widely accepted classification as follows: 1. Benign hemangioendothelioma,[1,6,18] also known as congenital hemangioma,[19] benign congenital hemangioma,[20] congenital capillary hemangioma,[15,21] infantile hemangioma or hemangioendothelioma,[22] congenital capillary angioma,[8] invasive hemangioma,[23] juvenile hemangioma,[24] and hypertrophic hemangioma;[25] 2. Cavernous hemangioma; and 3. True capillary hemangioma, a rare entity.

Case Report

Case 1:

An eight-year-old Saudi female presented with an increasingly enlarging, otherwise asymptomatic, left cheek swelling of two years' duration. Clinical examination revealed a diffuse, cystic, nontender, 5 cm diameter swelling occupying the left parotid region, pushing the left tonsil and soft palate medially. Cutaneous vascular malformation or nevi were absent. Complete blood count, coagulation profile and routine blood chemistry were normal. Parotid region plain x-rays showed a soft tissue mass with multiple calcific foci (Figure 1) with normal maxillae and mandible. Parotid region computed tomographic (CT) scan revealed a large mass 6 cm in diameter, nonenhancing on contrast, extending from the left temporomandibular joint to just below the angle of the mandible, bulging laterally as well as medially into the infratemporal region with multiple calcific foci (Figure 2).

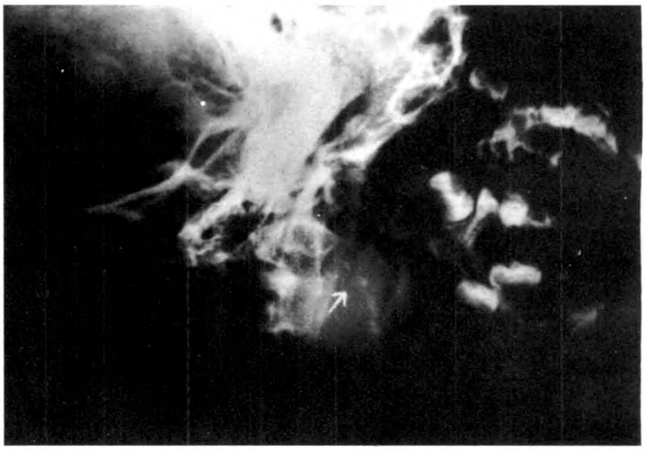

FIGURE 1. Plain x-ray with arrow demonstrating phleboliths as calcific spots in a patient with parotid hemangioma.

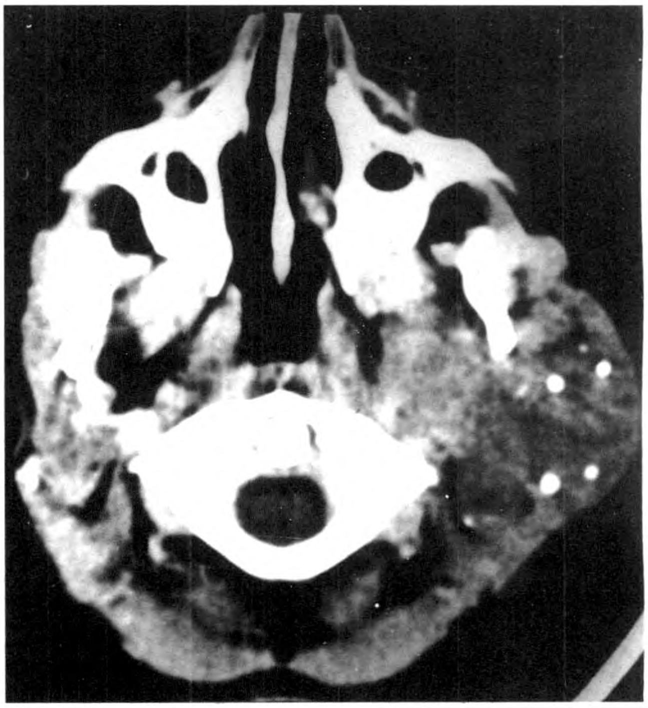

FIGURE 2. CT scan showing the intraparotid calcification that is strongly indicative of a hemangioma, when present.

From the Department of Surgery, College of Medicine, King Saud University, Abha Branch, Abha.

Address reprint requests and correspondence to Dr. Hamdi: College of Medicine, King Saud University, Abha Branch, P.O. Box 641, Abha, Saudi Arabia.

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encasing the styloid process. Bony destruction was absent Radiological diagnosis of hemangioma was made. Exploration revealed left parotid gland hemangioma occupying both lobes and extending into the infratemporal fossa. Using an operative microscope at 10x magnification, a total parotidectomy was performed with preservation of the facial nerve branches and complete excision of the vascular malformation. There was transient weakness of the marginal mandibular branch of the facial nerve with complete recovery by the second postoperative week. Histopathology showed normal parotid gland with dilated thrombi containing blood vessels. Multiple calcific areas were also seen. The patient has been free from recurrence with over one year of postoperative follow-up.

Case 2:

A 34-year-old Filipino male presented with a swelling in the left parotid region of five years' duration that suddenly became excruciatingly painful the night of admission with a marked increase in size, necessitating emergency room consultation. Examination revealed marked trismus, limiting fluid intake to small sips. The swelling was firm, warm, and tender. An admitting diagnosis of parotid tumor was made. Two hours post admission, a fine needle aspiration biopsy of the mass yielded hemorrhagic aspirate. Eight hours later the patient developed complete facial paralysis evolving over a one hour period.

Routine hematological, biochemical, and HIV investigations were normal. CT scan of the left parotid (Figure 3) showed a large, lobulated, isodense mass extending to the parapharyngeal space, displacing the pharyngeal mass medially. Exploration a few hours post admission revealed a hemangioma with an associated large hematoma deep to the facial nerve with compressed superficial lobe. A total parotidectomy with preservation of the facial nerve was done using the operating microscope. Histopathology revealed a cavernous hemangioma within the deep lobe of the parotid gland with extravasation of blood without phleboliths or calcific foci. Postoperatively, the patient was relieved of pain and trismus almost immediately and was on a normal diet within 24 hours. Follow-up electrophysiological conduction studies of the left facial nerve were normal from the fourth postoperative day. Clinical recovery of the left facial palsy occurred from the fourth postoperative week onward.

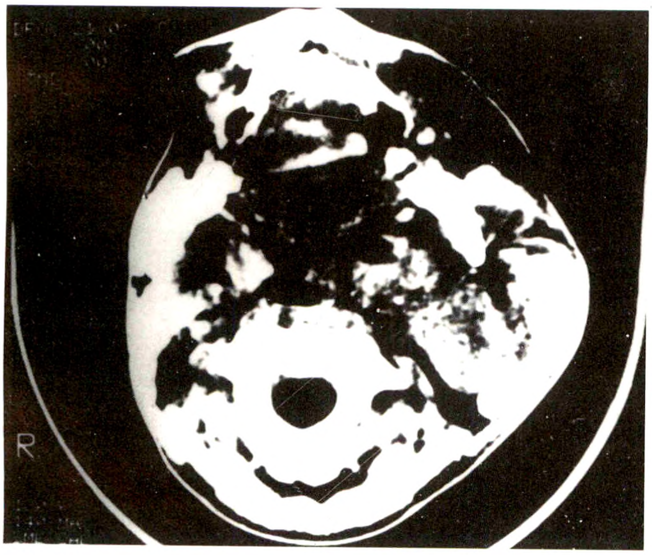

FIGURE 3. CT scan of a patient with cavernous hemangioma showing a homogenous mass in the left parotid region. Notable is the absence of any calcification.

Case 3:

A 28-year-old Yemeni male presented with a left cheek swelling present since birth and for which he had undergone two operations at different centers, one to excise the lesion and the other to ligate the left external carotid artery. At presentation he had a soft cystic swelling (4 cm x 5 cm) of the left cheek and parotid region with extension into the gingivobuccal sulcus. The patient also had smaller hemangiomata of the left conjunctiva. There was a scar over the left nasolabial fold and another over the left side of the neck (from previous external carotid artery ligation). Full hematological and biochemical investigations were normal. Plain x-rays of the left parotid region were normal, showing no calcification. Angiogram revealed a normal left internal carotid artery with complete occlusion of the left external carotid artery. At exploration, an extensive hemangioma involving the left parotid gland and extending to the infratemporal fossa was found. A total left parotidectomy with preservation of the facial nerve using operating microscope (10x magnification) was done. The involved masseter muscle was excised. A small extension of the lesion into the pterygoid musculature was identified but not removed. There was postoperative recovery with intact facial nerve function. At the one year follow-up, there was no recurrence although the left conjunctival hemangiomata had grown slightly larger. The histopathology showed features consistent with a diagnosis of cavernous hemangioma without foci of calcification.

Discussion

Cavernous hemangioma usually presents in late childhood or early adulthood and is unlikely to regress spontaneously or with conservative measures;[10,26] hence, the treatment of choice is surgical excision. This is also indicated because of the difficulty in distinguishing the lump from other parotid tumors.[26,27] There is also a risk of further and rapid enlargement of the tumor if left untreated,[28-30] causing pain or even suffocation of the patient.[16] There is no sex or side predilection.[10,17] Extralobular rather than intralobular connective tissue of the gland is involved.[17] The pulsatile flow in end arteries over a long period may cause the change of capillary hemangioma into a cavernous one.[10]

Parotid cavernous hemangioma may present as a solitary lump in the parotid region[26,28,29] or as a diffuse swelling.[11,31] It is usually soft but could be firm or sponge-like. Pain may or may not be present. The bluish discoloration of the overlying skin, characteristic of benign hemangioendothelioma is very rare with cavernous hemangioma.[20] There have been reports of associated cutaneous and regional hemangioma,[32] but these are uncommon.[9,11] The tumor may become visible and more easily palpable by tensing the masseter muscle when asking the patient to clench his teeth.[12] Rarely, the tumor may present as a pulsatile swelling within the parotid region[12] or with facial nerve palsy.[27] The lump may become more prominent when the head is bent forward or the patient lies horizontally[11] (turkey wattle sign). Masseteric hypertrophy[33] or trismus[34] could be a feature of parotid cavernous hemangioma. The presence of calcified phleboliths where normally no large venous plexuses occur is a characteristic x-ray finding in cavernous hemangioma of the salivary glands,[29] but are found in just over 15% of the patients and are comparable to changes in striated muscles[35] and gastrointestinal tract[36] with similar lesions. Occasionally, these phleboliths have been confused with salivary calculi.[11,37] Sialogram may demonstrate the mass as being separate from and displacing the duct system.[12,28,30]

The classical calcification was present in Case 1 and was evident on the plain x-ray. CT scan was used in two of our patients and was useful in delineating the extent of the tumor. Other authors have also found CT scan to be useful in the investigation of hemangioma.[38,39] We have no experience with magnetic resonance imaging (MRI) but Levine et al.[40] claim it to be superior to CT scan in the investigation of cavernous hemangioma.

Fine needle aspiration cytology has been advocated in the investigation of hemangioma[41,42] but in the only patient in whom we attempted it, the result was acute hemorrhage with facial nerve palsy. The cytological report was not helpful either. Arteriogram and venogram may be useful in delineating the hemangioma and may show the feeding and draining vessels. Martinez-Mora et al.[43] advocate the use of sialography, injection of methylene blue through Stensen's duct, location of the trunk of the facial nerve at its cranial origin, use of nerve stimulator, ligation of the external carotid artery and dissection of the branches of the facial nerve for safe total parotidectomy. Sialogram is not useful in distinguishing benign parotid tumors from malignant ones[5] but can be used to differentiate parotid from extraparotid masses.[44] We did not use sialography in any of our patients. Ligation of the external carotid artery was resorted to earlier in Case 3 and it did not help.

Total parotidectomy was performed in the three patients. Nerve stimulator was used in all three patients. The facial nerve and its branches were identified in all three patients and were preserved as far as possible. Operating microscope with a simple magnification of 10x was used in all patients and proved to be useful. We recommend its routine use in difficult parotid dissection.

Radiotherapy and sclerosing injections have no place in the treatment of cavernous hemangioma. The Chinese have claimed good results with a sclerosing solution called Xiao Zhi Ling.[45] Preoperative embolization of the hemangioma has been attempted[12,46,47] but is not widely used. There is a report of three patients whose parotid hemangioma disappeared with compression therapy,[48] but these are presumably hemangioendothelioma and not cavernous hemangioma.

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CHOLEDOCHODUODENAL FISTULA: A VANISHING COMPLICATION OF PEPTIC ULCER REVISITED

Mohamed A. Laajam, MB(Lond), MRCP(UK); Shawkat A. Zargar, MD, DM;
Ibrahim N. Al-Teimi, Facharzt; Kazi M. Kolar, MS;
Abdul Majeed A. Mohammed, FRCS(Glas); Ghulam M. Malik, MD

Spontaneous biliary-enteric fistula is a well recognized though uncommon disorder. Whereas cholecystoduodenal fistula accounts for 90% of biliary-enteric fistulas, the choledochoduodenal fistula (CDF) is a rarer type.[1,2] The majority of the former fistulas are caused by cholelithiasis, whereas 80% of CDFs are due to duodenal ulcer. Jaundice or cholangitis is a rare complication of duodenal ulcer-related CDF.[3,4] Most CDFs are discovered incidentally during a plain abdominal radiograph or an upper gastrointestinal barium series. Endoscopy has been used infrequently for visualization and delineation of the fistulous communication.[5,6]

The present reports describe two patients with duodenal ulcer that perforated into the common bile duct and subsequently was complicated by cholangitis in one patient. The role of endoscopy in the diagnosis of CDF is stressed. A review of the modern management of CDF is also outlined.

Case Reports

Case 1:

A 44-year-old Indian nonsmoking male doctor with a 10-year history of proven recurrent duodenal ulcer was referred to us for the evaluation of biliary-enteric fistula. He has been on regular H_2 antagonist medication for the last five years. He suffered three episodes of cholangitis during the previous 14 months. The investigations during the second episode of cholangitis at another hospital led to the suggestion of biliary-enteric fistula based on gas in the biliary tree on the plain radiograph of the abdomen (Figure 1) and ultrasonography. The upper gastrointestinal endoscopy showed grossly deformed duodenal bulb with an active ulcer and narrowing. An attempt at endoscopic retrograde cholangiopancreatography (ERCP) failed because of the duodenal narrowing. Upper gastrointestinal (UGI) barium series was not performed at this stage. The patient was given anti-ulcer therapy. Four months later, while on treatment, he developed another episode of cholangitis and was referred to us for evaluation one month later.

Physical examination was normal. Laboratory data showed elevated alkaline phosphatase 260 IU/L (normal <170 IU/L); serum amylase and gastrin levels were normal. The examination of UGI tract with pediatric fiberendoscope revealed grossly deformed duodenal bulb with narrowing and an active ulcer at the apex. An opening 2 mm in diameter was seen within the ulcer, through which bile and air were exuding, bathing the ulcer. The postbulbar area was entered with great difficulty and was normal. The opening was cannulated with a standard ERCP catheter and on injection of contrast, the common bile duct (CBD) was visualized along with the gallbladder (Figure 2). The duct was dilated to 12 mm with narrowing at its lower end and the gallbladder was normal. The CBD retained enough contrast one hour later to suggest delayed drainage (Figure 3). The ERCP was not possible to perform due to the degree of duodenal deformity and narrowing.

Surgery was performed which included gastrojejunostomy, vagotomy and Roux-en-Y choledochojejunostomy. The findings included chronic penetrated

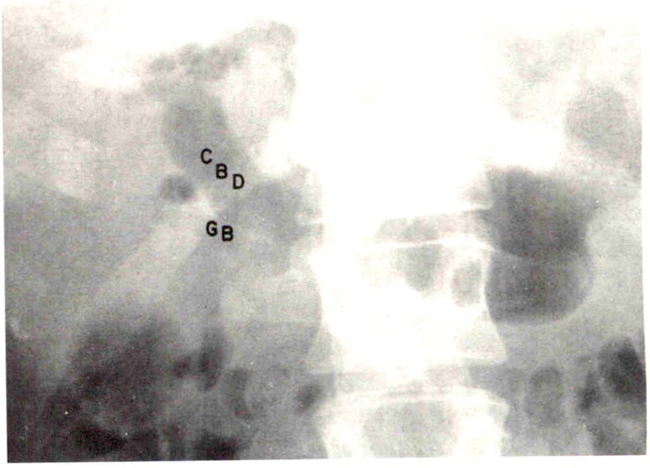

FIGURE 1. (Patient 1) Pneumobilia. Plain x-ray of abdomen showing air in the common bile duct (CBD), intrahepatic ducts and gallbladder (GB).

From the Department of Medicine, College of Medicine, King Saud University (Dr. Laajam); Riyadh Central Hospital (Drs. Zargar, Al-Teimi, Mohammed, Malik); Central Hospital, (Dr. Kolar) Qatif.

Address reprint requests and correspondence to Dr. Laajam: Department of Medicine (38), King Saud University, College of Medicine, P.O. Box 2925, Riyadh 11461, Saudi Arabia.

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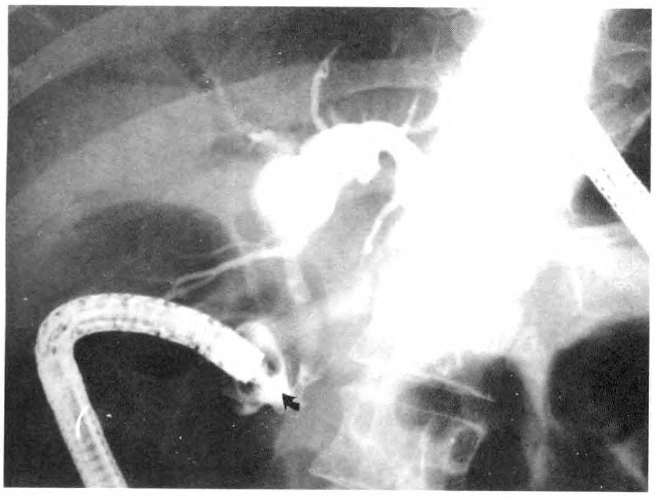

FIGURE 2. (Patient 1) Endoscopic cholangiogram through the fistula (arrow) in the duodenal bulb.

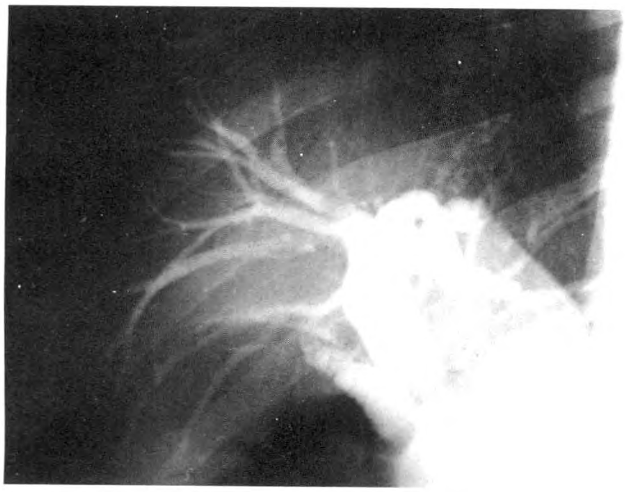

FIGURE 3. (Patient 1) Cholangiogram half an hour after injection of contrast, showing retention of contrast in dilated biliary tree.

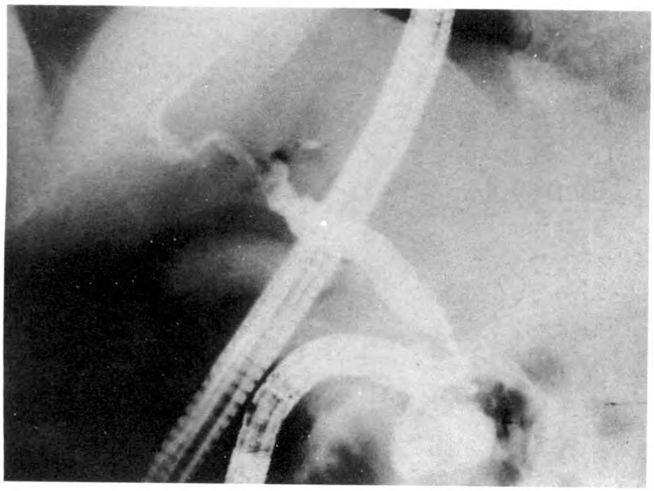

FIGURE 4. (Patient 2) Endoscopic cholangiogram through the fistula opening in the duodenal bulb.

duodenal ulcer with narrowing of the lower end of the CBD.

Case 2:

A 56-year-old Filipino male was admitted to our hospital with a history of two weeks of recurrent attacks of epigastric pain and retrosternal heartburn associated with vomiting of small amounts of coffee ground material on the day of admission. He had no melena. Symptoms were relieved by antacids. Apart from a similar attack for a short time one year earlier, the patient had been in good health and symptom-free. He is a nonsmoker and there is no history of ethanol abuse or NSAIDs medication.

Physical examination showed a healthy appearing male with stable vital signs and only mild epigastric tenderness.

Laboratory data showed Hb 13.4 and normal platelets, coagulation and biochemistry profiles. HBsAg was positive. A provisional diagnosis of mild UGI bleeding secondary possibly to peptic ulcer disease or reflux esophagitis was made. An early UGI endoscopy showed a large mixed type of hiatus hernia and otherwise normal stomach. The duodenal cap was grossly deformed and contracted. A large chronic active ulcer was present in the posterior wall of the cap, with no evidence of bleeding. However, there was an adjacent small opening through which bile was exuding. The second part of the duodenum was reached with difficulty and was normal. A biliary-duodenal fistula was suspected. Under x-ray screening, air was seen in the gallbladder and, on cannulation of the opening and injection of contrast medium, dye was seen filling the CBD and later the GB (Figure 4). A final diagnosis of a chronic penetrating duodenal ulcer causing CDF was established. A barium meal subsequently confirmed the presence of the large hiatus hernia, duodenal cap ulcer and gross deformity, but no barium was seen in the biliary tract. The patient was started on H_2 blocker treatment and was prepared for surgery for repair of the hiatus hernia and peptic ulcer disease complications. Nissan fundoplication, truncal vagotomy and gastrojejunostomy were performed one week later. After an uneventful postoperative recovery, the patient was discharged home symptom-free and continued on H_2 blocker therapy for long-term treatment. Unfortunately, he failed to attend for follow-up.

Discussion

Choledochoduodenal fistula comprises 4% to 20% of all spontaneous enterobiliary fistulas; 80% of these are secondary to penetrating duodenal ulcer erosion from the first portion of the duodenum into the lower end of the common bile duct.[2,5,6] The sex distribution is representative of the duodenal ulcer population, i.e., three times more common in males than females. Other less common causes of CDF include cholelithiasis, operative trauma, duodenal diverticula, Crohn disease, and neoplasms of the stomach, duodenum, ampullary region and distal common bile duct.[2]

The search of the English literature in the past decade failed to reveal a case of duodenal ulcer-induced CDF possibly due to the availability of potent ulcer-healing drugs.

The clinical features of CDF due to duodenal ulcer usually cannot be distinguished from those of uncomplicated duodenal ulcer disease; the ulcer, however, may be resistant to medical therapy. The alkaline bile bathing the ulcer has been suggested to relieve the pain by neutralizing the acid.[3] Cholangitis, jaundice or abnormal liver functions are rare in CDF.[2,5,6] This was the presenting problem in our first patient and was the result of development of the stricture at the lower end of the common bile duct.

The incidental demonstration of gas in the biliary tree on plain radiograph of the abdomen or the entrance of barium into the biliary tract during barium UGI series may provide the first suspicion of CDF. Indirect biliary imaging such as oral cholecystography or IV cholangiography is not diagnostic. Fiberoptic endoscopy with direct visualization of an ulcer and the alimentary side of the fistula with its subsequent cannulation to define the normal and pathological anatomy remains an excellent tool in experienced hands. While ERCP may be difficult due to associated ulcer and duodenal deformity, a satisfactory examination can be performed with pediatric-size endoscope as performed in the present cases.[5,6]

Until recently, the treatment of CDF due to duodenal ulcer was controversial. However, with the advent of potent anti-ulcer drugs, healing of ulcers has been shown to be associated with healing and closure of fistulas as well.[5,6] Endoscopic bile duct stenting combined with an anti-ulcer therapy leads to the satisfactory healing of the fistula as well. This mode of endoscopic treatment has been found effective in patients with other forms and causes of biliary fistulas such as those following cholecystectomy.[7] Surgery is indicated in those who have a complication of the duodenal ulcer including perforation, hemorrhage, stenosis or intractability, or those who have associated biliary sequelae.[2,5,6] Vagotomy and gastrojejunostomy or exclusion-type gastrectomy are optimal. This was the case in both of our patients. Excision of the fistula is not warranted and is hazardous since long-term complications of untreated fistulas are rare. Some type of internal biliary drainage will be needed in patients with cholangitis or biliary stricture, as in our case.

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REACTIVE HEMOPHAGOCYTIC SYNDROME: A REPORT OF TWO CASES FROM KUWAIT

Soad Al-Bahar, MRCPath; Ramesh Pandita, MD;
Boman N. Dhabar, MD; Ramesh Kumar, MD, PhD

Reactive hemophagocytic syndrome (RHS) is a clinicopathological entity characterized by acute onset, fever, lymphadenopathy, hepatosplenomegaly, pancytopenia and reactive histiocytosis with striking hemophagocytosis. The syndrome occurs predominantly in immunocompromised patients and is usually fatal.[1,2] The disorder is rare in apparently immunocompetent patients with variable outcome.[1,2] The etiological agents incriminated have been predominantly viruses.[1,3,4] Nonviral infections such as tuberculosis[5] and bacterial infections[1,2] have been other major causes. We describe two cases of hemophagocytic syndrome in apparently nonimmune suppressed patients who had uneventful complete recovery and highlight variable bone marrow morphology and the need for differentiating it from hematological disorders such as myelodysplastic syndrome and hypoplastic anemia.

Case Reports

Case 1:

A 12-year-old Kuwaiti female presented in February 1990 with a five-day-history of fever, weakness and generalized aches and pains. Physical examination revealed cervical and axillary lymphadenopathy, splenomegaly of 3 cm and hepatomegaly of 2 cm below the costal margin (bcm). Hemogram showed Hb 8.2 g/dL, WBC 3.2×10^9/L, platelets 110×10^9/L, differential count of polymorphs 19%, lymphocytes 60%, monocytes 11%, eosinophils 1%, atypical lymphocytes 9%. Red cell morphology was normocytic normochromic and reticulocyte count was 1%. Serum chemistry including liver function tests and the coagulation screen were normal. Bone marrow aspiration revealed normal cellularity, hyperplastic erythropoiesis, normal maturation of granulocytic series and adequate megakaryocytes. There was an increase in macrophages, many exhibiting striking hemophagocytosis (Figure 1). Blood, urine, and throat cultures, serological tests for Epstein-Barr virus, herpes simplex virus, cytomegalovirus and hepatitis B virus were negative. The patient was treated with supportive care consisting of concentrated red cell transfusion and antibiotics. She had an uneventful recovery with regression of organomegaly and lymphadenopathy, and complete blood counts returned to normal. The patient refused a repeat bone marrow examination. Her serum immunoglobulins estimated after recovery have been normal. She continues to be well two years hence, with no hematological abnormalities or relapse of the hemophagocytic syndrome.

Case 2:

A 47-year-old Kuwaiti female presented in November of 1992 with a 10-day-history of high grade fever, generalized body aches and increasing weakness. She had no history of drug ingestion. Physical examination revealed pallor and nontender splenomegaly of 7 cm bcm. Investigations showed Hb 8.1 g/dL, WBC 1.8×10^9/L, platelets 45×10^9/L, differential count of polymorphs 1%, lymphocytes 97%, atypical lymphocytes 2%. Liver function tests revealed elevated serum glutamyl pyruvate transferase (71 U/L) and gamma glutamyl transferase (169 U/L). The remainder of the serum chemistry and coagulation screen were normal. Bone marrow aspirate

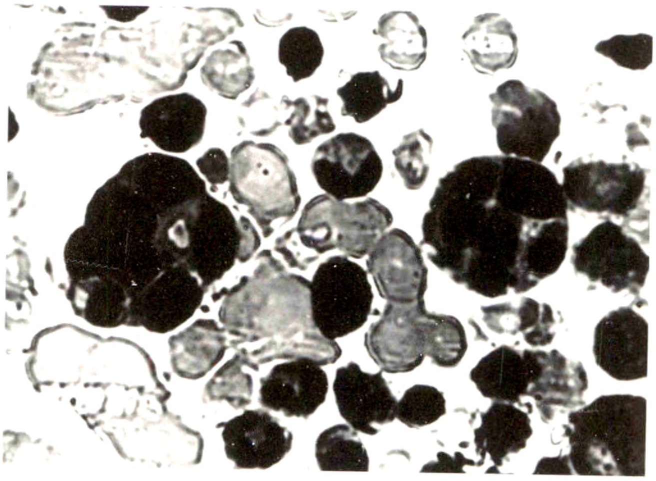

FIGURE 1. Marked hemophagocytosis predominantly of erythroblasts. Leishman stain.

From the Department of Hematology (Drs. Al-Bahar, Pandita, Dhabar), Kuwait Cancer Control Centre and Department of Hematology (Dr. Kumar), Al-Adan Hospital, Al-Shamiya.

Address reprint requests and correspondence to Dr. Al-Bahar: Consultant Hematologist, P.O. Box 12391, Al-Shamiya 71654, Kuwait.

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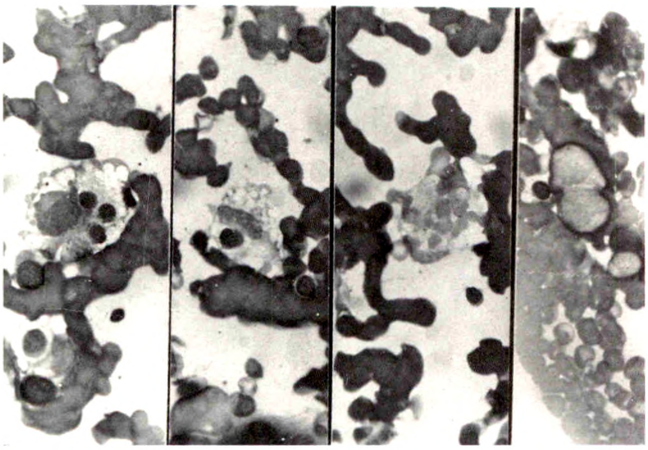

FIGURE 2. A composite showing hemophagocytosis by reactive macrophages and presence of blast cells. Leishman stain.

revealed normal cellularity, depressed erythropoiesis, increased blasts (12%), marked paucity of differentiated myeloid forms, megakaryocytic hyperplasia and rare dysplastic megakaryocytes. There was a striking increase in macrophages, many of which exhibited hemophagocytosis (Figure 2). The iron staining did not reveal ringed sideroblasts. Repeat bone marrow aspiration and biopsy performed three days later revealed markedly hypoplastic bone marrow with trilineage hypoplasia; however, plasma cells were prominent and occasional macrophage showed hemophagocytosis (Figure 3). Cultures for aerobic and anaerobic organisms were negative and serological studies for Epstein-Barr virus, herpes simplex virus, cytomegalovirus, human immunodeficiency virus and hepatitis B virus were negative. Protein electrophoresis and serum immunoglobulin profile were normal. She was treated with supportive care consisting of concentrated red cell transfusion and antibiotics. She had an uneventful recovery in two weeks and her hemogram revealed Hb 11.1 g/dL, WBC 9.3×10^9/L, platelets 251×10^9/L and normal differential count. Repeat bone marrow and biopsy performed after 3-1/2 months and six months of her initial presentation revealed a normal bone marrow with no evidence of myelodysplasia or hemophagocytosis (Figure 4).

Discussion

In 1979,[1] Risdall et al. first introduced the term, "virus associated hemophagocytic syndrome" and laid down criteria for its separation from malignant histiocytosis. The syndrome is characterized by high fever, constitutional symptoms, lymphadenopathy, hepatosplenomegaly, skin rashes, pancytopenia, liver function and coagulation abnormalities. The pathologic hallmark of this condition is benign histiocytic proliferation and striking hemophagocytosis in the bone marrow and lymph nodes. Our patients had the described clinical findings though both lacked skin rash, while one had no lymphadenopathy. The bone marrow findings were characterized by striking hemophagocytosis and benign histiocytic proliferation. In Case 1, the bone marrow was normocellular with erythroid hyperplasia in contradistinction to more frequent hypocellularity and erythroid hypoplasia reported in the literature;[1] this may be due to the fact that bone marrow examination was performed in the recovery phase when hyperplastic marrow with persistent hemophagocytosis can be seen.[1,2]

In Case 2, the initial bone marrow morphology revealed features simulating myelodysplastic syndrome (MDS), i.e., increase in myeloblasts, depletion of mature myeloid forms, erythroid hypoplasia, and rare dysplastic megakaryocytes. Although reactive hemophagocytosis has been reported with MDS,[2] the presence of striking hemophagocytosis should warrant a careful follow-up as reversal of pancytopenia and bone marrow morphological changes help in excluding MDS, as in our case. The apparent increase in the blasts may have been due to the initial selective phagocytosis of the differentiated myeloid cells.

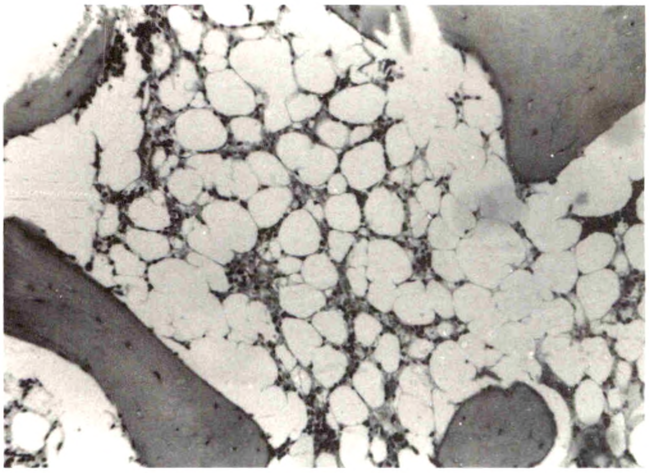

FIGURE 3. (Case 2) severe bone marrow hypoplasia; few lymphocytes and plasma cells are present. (Case 2) hematoxylin and eosin.

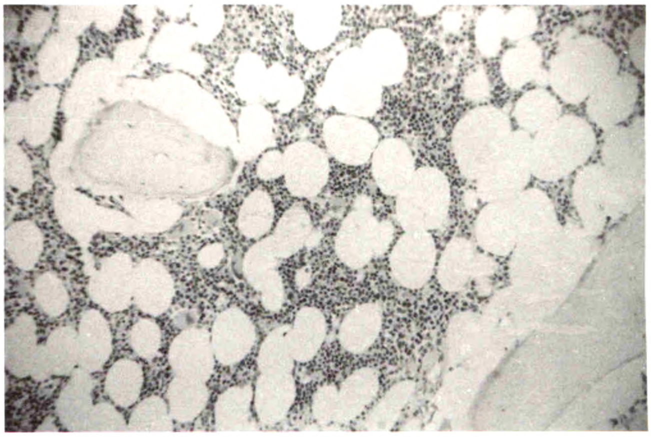

FIGURE 4. Normal bone marrow. (Case 2) hematoxylin and eosin.

Sequential bone marrow aspiration and trephine biopsy in this patient revealed severe hypoplasia with mild hemophagocytosis simulating aplastic anemia. Although hypoplasia is common,[1] the presence of severe hypoplasia may cause diagnostic difficulties if the patient is seen for the first time in this stage; however, the presence of hemophagocytosis should serve as a marker and prevent the use of any unnecessary immunosuppressive therapy as these patients may recover completely, both clinically and hematologically.

The most common etiological agents causing this syndrome are viruses, predominantly the herpes group of viruses, including Epstein-Barr virus, herpes simplex and cytomegalovirus.[1,3,4,6] Similar cases have been reported to be associated with nonviral infections such as tuberculosis[5] and gram positive and gram negative bacteria.[2,7] A search for these etiological agents was conducted in our patients, but no agent could be identified. It is possible that an unidentified virus was responsible. Infection-associated hemophagocytic syndrome is most common in immunocompromised patients such as renal transplant patients[1] and lymphoma patients.[2] The occurrence of hemophagocytic syndrome in apparently immunocompetent patients may be explained on the basis of transient immunoparesis. It has been suggested that altered T-cell function results in production of large amounts of gamma interferon and other lymphokines that cause macrophage activation and consequent hemophagocytosis.[8] Cytopenias are possibly secondary to hemophagocytosis and bone marrow failure. The bone marrow hypoplasia may be due to direct effect of viruses on the hemopoietic cells.[1] The role of altered T-cell function and cytokines in the development of hypoplasia in RHS needs further study.

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EHLERS-DANLOS SYNDROME ASSOCIATED WITH OLLIER DISEASE

Mohammed Moussa, MCh(Ortho), PhD; Anwar Ul-Haque, FCAP; Ake Ahlberg, PhD

The association of Ehlers-Danlos syndrome (EDS), a hereditary disorder of connective tissue, and Ollier disease, a rare, nonhereditary form of bone dysplasia, in a five-year-old female, is described. This association has not been reported before. The possibility of a common etiological factor is discussed.

Case Report

A five-year-old Syrian female presented with limping. She had a true shortening of the right lower limb of 4 cm. The skin was hyperextensible (Figure 1) but normal in texture. Joint hypermobility was prominent in the hands (Figure 2), feet and knees. She had 35° and 15° genu recurvatum for the right and left knee respectively (Figure 3). Sclerae, fundi, cornea, teeth and palate were normal. Two systolic clicks and a late systolic murmur were audible at the cardiac apex. The cardiac murmur increased in intensity on squatting, indicating asymptomatic mitral valve prolapse.

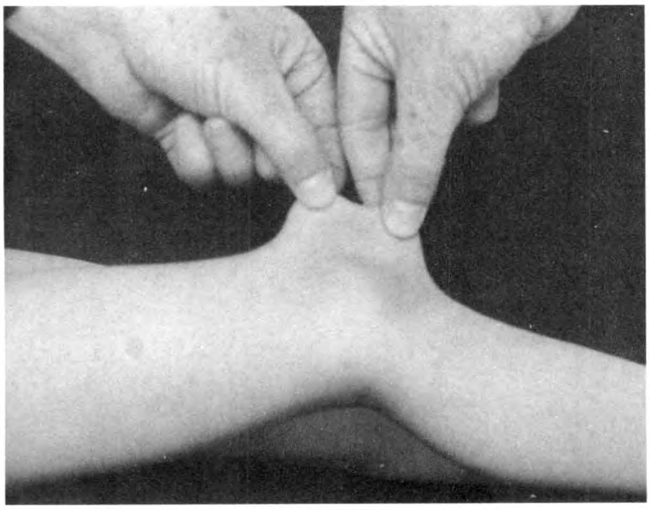

FIGURE 1. Moderate skin hyperextensibility at the knee.

The parents were consanguineous first cousins. The father had no clinical features of EDS. The mother and two brothers (twins) showed varying degrees of joint and skin hyperextensibility.

Routine hematological and clinical chemistry tests were normal. The electrocardiogram and cardiac echo Doppler studies could not rule out a mitral valve prolapse.

Radiographic skeletal survey revealed multiple radiolucent islands in the proximal and distal right tibia. The distal right femur showed large radiolucent metaphyseal lesions. The cortex was thin and expanded. Pathognomonic longitudinal "fanlike" linear densities

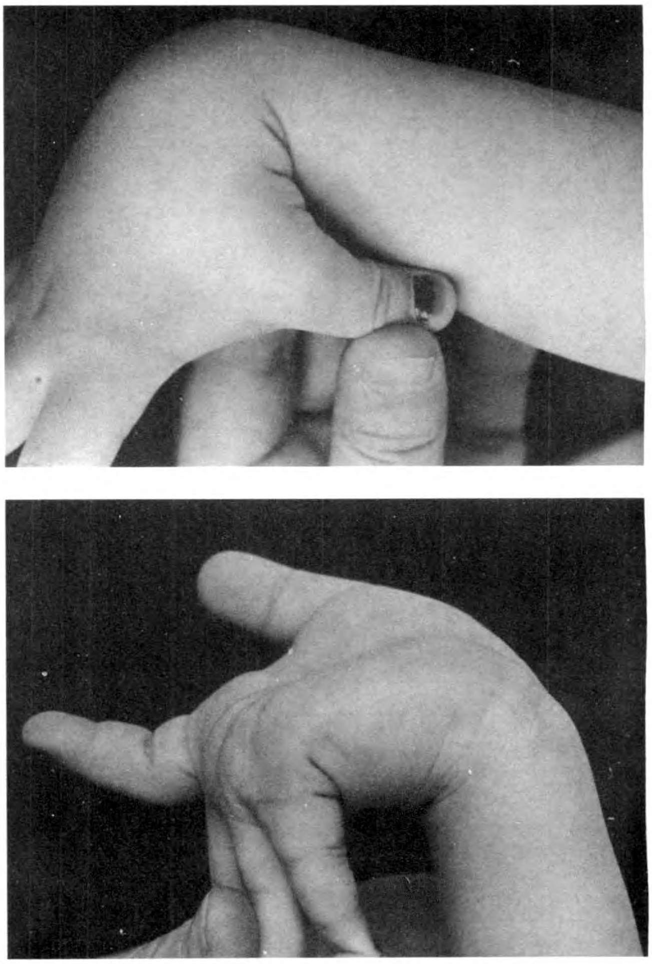

FIGURE 2. Marked hypermobility of the small joints of the hand. a) the thumb touches the forearm; b) more than 90° hyperextension in metacarpophalangeal joints.

From the Departments of Orthopedic Surgery (Drs. Moussa and Ahlberg) and Pathology (Dr. Ul-Haque), King Fahd Hospital of the University, Al-Khobar.

Address reprints and correspondence to Dr. Moussa: Department of Orthopedic Surgery, King Fahd Hospital of the University, Department of Orthopedic Surgery, P.O. Box 40194, Al-Khobar 31952, Saudi Arabia.

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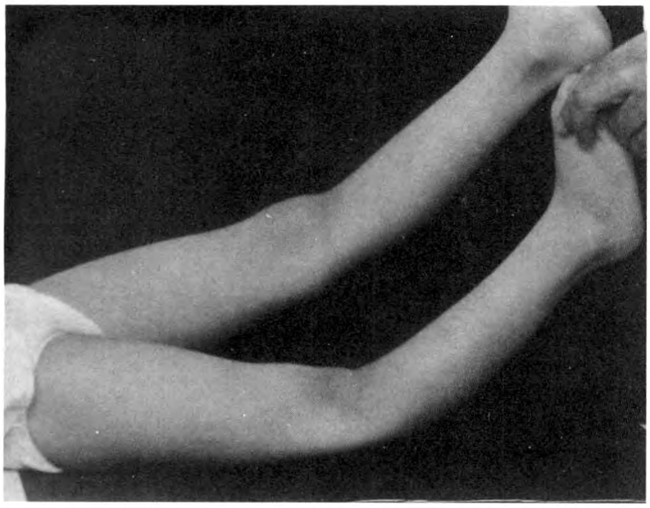

FIGURE 3. Marked hyperextension of knee joints.

admixed with radiolucent cartilaginous columns were seen (Figure 4). Skull, spine, pelvis, hands and feet were normal.

The skin and the femoral lesion were biopsied. The tissue excised from the femur was firm, grayish white and gritty. No abnormal bleeding occurred during or after the operation. The incision healed normally. Microscopy of the skin and bone biopsies were consistent with EDS and Ollier disease respectively (Figures 5 and 6).

Discussion

Defects in the collagen metabolism are the cause of EDS. The manifestations of the syndrome vary depending on the metabolic defect and which of at least 11 known collagen types are affected. Nine types of the syndrome are now accepted.[1] Categorization is, however, not always possible. The patient described in this report had an autosomal dominant inheritance pattern. The main symptoms were marked joint hypermobility, moderate skin hyperextensibility and a systolic murmur suggestive of mitral valve prolapse. These clinical features are consistent with EDS type III.[1]

Although collagen is an essential component of bone tissue, bony changes are unusual in EDS. The association with osteogenesis imperfecta[2] and monostotic fibrous dysplasia[3] has been reported. The simultaneous presence of two rare diseases could be coincidental due to a spontaneous mutation or caused by a common etiological factor.[4-6]

Although a spontaneous mutation cannot be ruled out, the fact that the mother and twin brothers had varying degrees of skin elasticity and joint hyperextensibility "expressivity" strongly suggests an autosomal dominant pattern of inheritance in this case.

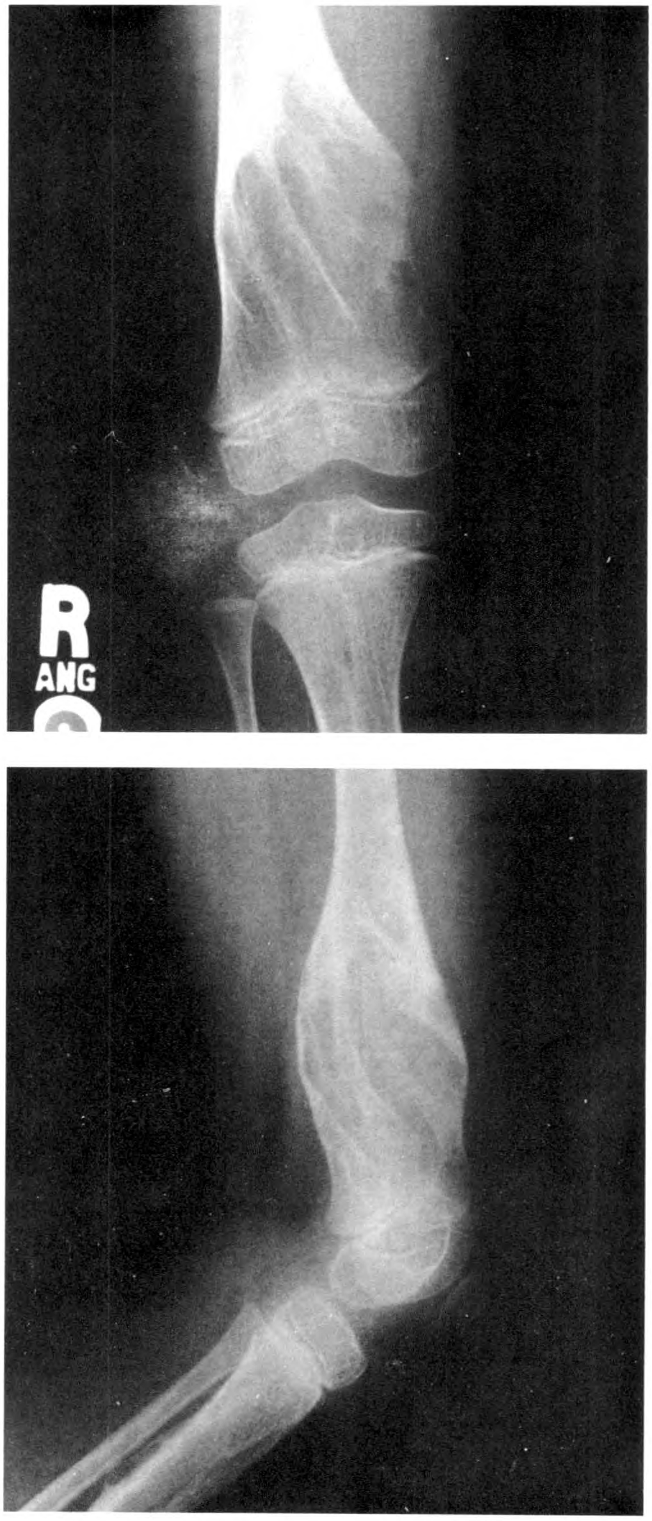

FIGURE 4. Radiogram of the distal right femur and proximal right tibia showing characteristic "fanlike" linear densities and radiolucent cartilaginous columns. a) AP view; b) lateral view.

The growth plate of growing bone displays crucial synchronized activities of fibrous, osseous and chondroid tissues at ossification groove and perichondrial ring.[7] An aberration in these synchronized activities secondary to a primary collagen defect may cause collagen weakening and chondroid hyperplasia. Type X collagen, a biosynthetic

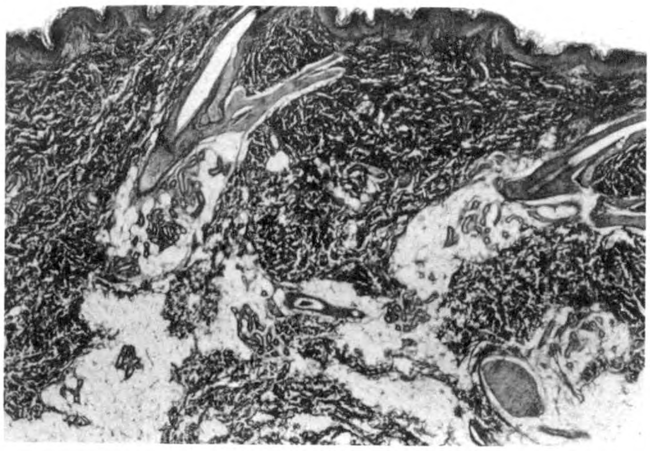

FIGURE 5. Skin biopsy revealing proportional increase in elastic fibers consistent with EDS (elastic van Gieson stain 100x).

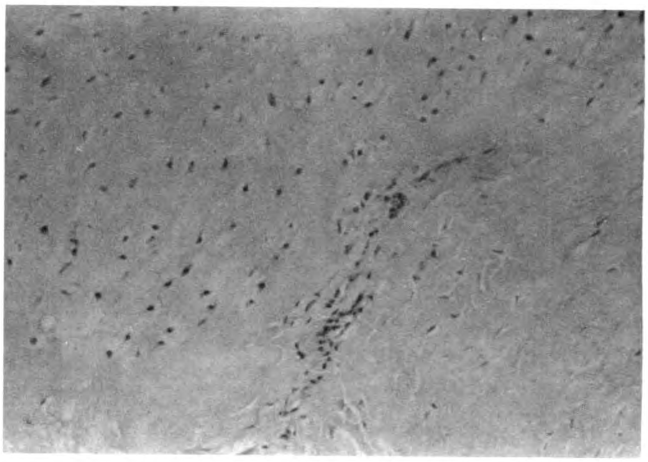

FIGURE 6. Femoral lesion biopsy showing enchondroma rimmed by mature collagen tissue (arrow) (hematoxylin and eosin stain 100x).

product of growth plate hypertrophic chondrocytes, plays an important role in the process of endochondral ossification.[4] Ollier disease is supposed to be due to a defect in this process.[6] An enzyme defect at any of the various steps of type X collagen synthesis may thus be a common factor in our case. Similar aberrations have been suggested to explain association of EDS with osteogenesis imperfecta and fibrous dysplasia.

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Letters to the Editor

The *Annals of Saudi Medicine* welcomes *Letters to the Editor* from its readers. They may be on any topic, though the Editor especially encourages discussion of papers published in the *Annals*. Letters should be no more than 100 typewritten lines in length, typed double-space, and submitted in triplicate. Letters may include one figure or brief table and up to five references. Submission of a letter constitutes permission for the *Annals* to use it for publication. Letters should not duplicate similar material being submitted or published elsewhere, and the *Annals* reserves the right to edit letters submitted. Letters referring to a recent *Annals* article should be received within six weeks of the article's publication.

Prevalence of Hepatitis B Surface Antigenemia Among Patients with *Schistosoma mansoni*

To the Editor: I read the recent paper by Dr. Hussein M. Al-Freihi, "Prevalence of hepatitis B surface antigenemia among patients with *Schistosoma mansoni*" with interest,[1] and congratulate him for using epidemiological methods, that is, the case-control study, for investigating endemic diseases.

However, I believe his conclusion, "...patients with *Schistosoma mansoni* are exposed to a higher risk of acquiring HBV infection and ..." is reversed. It is true that farmers and males have more exposure to either infection than city dwellers and females in the Middle East; and when parenteral therapy was used to treat schistosomiasis, some patients may have been infected with HBV through contaminated needles.[2] However, a recent study in Egypt, in which subjects were selected because they had acute viral hepatitis, showed that patients having concomitant *Schistosoma mansoni,* which was usually asymptomatic, were much more likely to become chronic HBsAg carriers than other subjects with acute viral hepatitis who did not have active *S. mansoni* infections.[3] Among the 95 patients with acute HBV hepatitis, the HBsAg carrier rate was 25% in those with - and 9% in those without - concomitant *Schistosoma mansoni*, a significant ($P<0.038$) difference. In addition, patients with *Schistosoma mansoni* having acute viral hepatitis - caused by HBV, hepatitis delta virus on top of HBV infection and (probably) hepatitis C virus infection (which is prevalent in Egypt) - had greater prevalence of, and more prolonged, splenomegaly and morbidity (graded by clinical outcome and liver function tests) than others with acute viral hepatitis not having active schistosomiasis.

I am unaware of any study proving patients with *Schistosoma mansoni* have a greater risk of HBV infection, as Dr. Al-Freihi concluded,[1] although two others have shown that HBsAg carriage is prolonged in patients with both infections.[4,5] This is also biologically plausible since *Schistosoma mansoni* infections affect the immune response in two ways that might delay clearance of viral infections. Anti-idiotype antibodies produced in patients with chronic schistosomiasis can down-regulate specific immune responses and suppress nonspecific immune responses.[6] In addition, recent very interesting studies in mice and humans have shown that *S. mansoni* egg antigens modify subpopulations of thymus helper cells. Th2 activity and the cytokines involved with eosinophilia and IgE secretion are stimulated while Th1 activity and the cytokines, interleukin 2 and gamma interferon, as well as $CD8^+$ cytotoxic T cells, components of the immune system that help clear viral infections, are down-regulated in BALB/c mice infected with *S. mansoni.*[7] The immunosuppression appears specific, possibly organ (liver) associated, since schistosomiasis has not been reported to increase the prevalence of HIV infection or decrease the time from initial infection to the development of AIDS.

G. Thomas Strickland, MD, PhD, DCMT
Professor and Director
International Health Program
University of Maryland
School of Medicine
Baltimore, MD, 21201, USA

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Reply

To the Editor: I wish to thank Dr. GT Strickland for his interest in my paper on prevalence of hepatitis B surface antigenemia among patients with *Schistosoma mansoni.*[1] It is true that the exact infection rate and therefore the risk of hepatitis B virus (HBV) infection among schistosomiasis patients remains unknown. However, the frequent association between the two infections has been established beyond any doubts.[2-7] It is interesting to note that 81% of patients with uncomplicated schistosomiasis reported by Madwar et al.[2] had markers for past or present HBV infections. They postulated that this high rate of infection is due to parenteral treatment of schistosomiasis patients with antimony compounds using inadequately sterilized needles and syringes, yet only 38 of 85 (45%) patients with a mean age of less than 20 years can recall receiving such treatment. In a recent study[8] involving patients with schistosomiasis who received Praziquantel, increased risk of contracting HBV infection was again demonstrated. Furthermore, it is generally accepted that patients with concomitant infections of *S. mansoni* and HBV are more likely to develop more serious liver disease and become chronic HBsAg carriers and thus deserve to have special medical attention including priority to receive HBV vaccine as I concluded.

Hussein Al-Freihi, MD
Medical Director
Social Insurance Hospital
P.O. Box 42142
Riyadh 11541, Saudi Arabia

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Juvenile Myoclonic Epilepsy in Association with Nonprogressive Mental Subnormality

To the Editor: Juvenile myoclonic epilepsy (JME) is a nonprogressive epileptic disease with prevalence of 5% to 11% among other forms of epilepsy.[1-5] It is an age-related idiopathic form of generalized epilepsy with characteristic clinical and electroencephalographic (EEG) findings.[2] JME appears around puberty and is characterized by seizures with irregular myoclonic jerking, often with generalized tonic clonic seizures (GTCS) and less frequently, absences. Despite its specific features, JME is often underdiagnosed worldwide.[2-7] Being an idiopathic form of epilepsy, the mental and neurological examination should be normal.[2]

TABLE: *Patients' data.*

Patient No.	Age in years	Sex	Age of onset of epilepsy	Age MS noted	EEG	CT-brain	IQ	Follow up in years
I	19	F	10	9	Normal	Normal	60	7
II	22	F	18	12	Theta + ** SMSSW	Normal	75	5
III	18	M	8	8	** SMSSW *** +PS	Normal	65	4

*=MS:mental subnormality; **=SMSSW: spike-multiple-spikes-slow waves; ***=PS: photosensitive; EEG=electroencephalographic; CT=computed tomography; IQ=intelligence quotient.

In a prospective study of 70 patients with JME, three additional patients were encountered who comply with the diagnosis of JME except for an associated mental subnormality. The data obtained in the three patients are noted in the table.

JME was manifested as myoclonic jerking and GTCS. The neurological and neuro-ophthalmological assessments were normal in all the patients. The neurometabolic screen for neurologic conditions occurring in such age group, including Lofra's bodies, were negative. No mental deterioration was observed for a follow-up period of four to seven years. The recent and the remote histories of the patients did not suggest an underlying etiology for the mental subnormality. Drug history did not incriminate anticonvulsant-related cognitive disorder in the three patients. There was no history of GTC status epilepticus. None of the patients completed the junior primary school education.

The proposal for revised classification of epilepsies and epileptic syndromes serves as a useful guideline, though it may be difficult at a particular time to place the patient in a particular syndrome.[2] Our three patients, in the presence of mental subnormality, could not be classified as JME according to the International League Against Epilepsy (ILAE) proposal.[2] Initially progressive myoclonic epilepsy was suspected and only time could tell the static nature of the mental subnormality, which could be coincidental. Recognition of such patients is important, as progressive myoclonic epilepsy could be erroneously diagnosed with its serious implications. On the other hand, early diagnosis of such cases will help in proper school placement and this may increase their social competence in different walks of life.

Tahir Obeid, MRCP(UK)
Ghazala Waheed, MB, BS
Social Insurance Hospital
P.O. Box 42142
Riyadh 11541, Saudi Arabia

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Cytologic Diagnosis of Malacoplakia

To the Editor: Malacoplakia is a rare chronic inflammatory process characterized histologically by the collection of histiocytes with acidophilic granular cytoplasm, so-called von Hansemann cells, some of them rounded lamellar basophilic inclusions in the cytoplasm called Michaelis-Gutmann bodies or calcospherites. In 1902, Michaelis and Gutmann described malacoplakia in the urinary tract and until the last two decades, it was thought to be confined to the urinary tract, when cases in other sites were reported. The exact etiology of malacoplakia is not known but an acquired defect of intracellular degradation of ingested bacteria, usually gram negative coliform bacilli, by phagocytes has been postulated as an etiologic factor.[1]

Twenty-two cases of malacoplakia affecting the genital tract have been previously reported, but only in two cases, cytologic analysis has been included. We reported the cytological findings in a case of malacoplakia involving the vagina, cervix, endometrium, parametrium, one adnexa and the skin.

A 50-year-old Saudi female, Para 9, Gravida 10, 11 years postmenopausal, was referred to the Maternity and Childrens Hospital (Riyadh) because of sluggish vaginal bleeding associated with lower abdominal pain for one year. On admission, she was a thin female, with a temperature of 39°C, BP of 130/80. Physical examination was noncontributory except for a hard, painful mass in the lower abdomen. Gynecological examination revealed an enlarged uterus, a necrotic polypoid mass at the cervix and vaginal vault and an irregular nodular mass on the right side of the uterus. Biopsy and cytologic smear from the vaginal lesion were obtained.

The cervical smear showed an inflammatory exudate made up of histiocytes with polymorphonucleocytes (PMN) associated with a scanty number of epithelial cells as expected in postmenopausal Papanicolaou smear.

In addition to the increased number of histiocytes with fine granular cytoplasm and intracytoplasmic bacteria, a thin layer of capillary blood vessels lined by endothelial cells was present. Occasional target-like inclusions of Michaelis-Gutmann bodies were observed (Figure 1). A cytologic diagnosis of malacoplakia was made. This was later confirmed by the biopsy obtained from the vaginal mass (Figure 2). Subsequent total hysterectomy revealed that the process was extensively involving the cervix, endometrium, parametrium and one adnexa also.

The clinical presentation in this patient is the classic manifestation of malacoplakia involving the genital system. The patients are 50 years old or older and the main complaint is usually vaginal bleeding because the vagina is the most commonly affected organ.[5] Clinical diagnosis of carcinoma also is frequently made when the lesion is affecting the cervix.[4,6] The cervical smear revealed an inflammatory process with PMN and histiocytes associated with strings of capillary structures and postmenopausal epithelial changes. The histiocytes were filled with bacteria and a few Michaelis-Gutmann bodies were present in the histiocytes.

Cytologic diagnosis of malacoplakia is important because the condition is rarely suspected clinically, and a

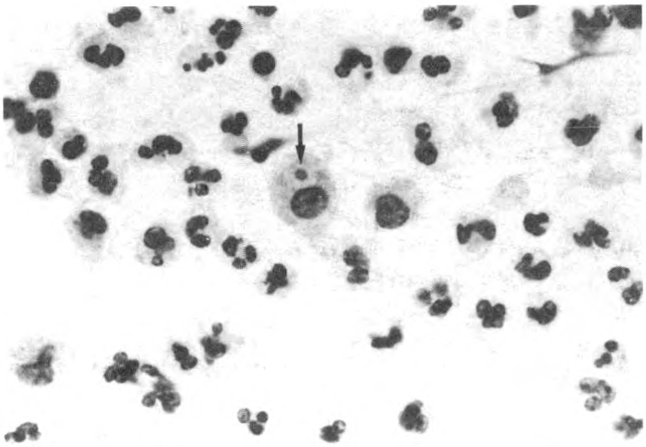

FIGURE 1. A Michaelis-Gutmann body is clearly observed in the cytoplasm of a histiocyte in this microphotograph. Papanicolaou stain. Original magnification 400x.

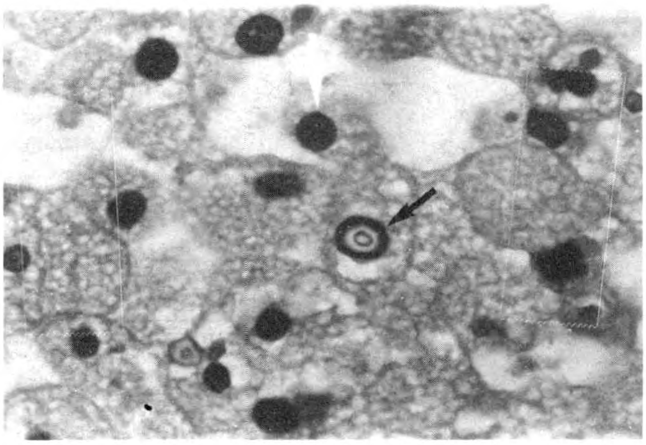

FIGURE 2. The microphotograph shows cluster of histiocytes (white arrow), one of them with a clear Michaelis-Gutmann body (black arrow). Hematoxylin & Eosin stain. Original magnification 400x.

misinterpretation as nonspecific inflammation may delay therapy. The clues to recognize malacoplakia in cytological preparation were excellently described by Stewart and Thomas[10] and summarized as follows: 1) inflammatory process with an increase of histiocytes; 2) finely granular macrophages with bacteria and Michaelis-Gutmann bodies; 3) thin capillary structures.

The pathognomonic Michaelis-Gutmann bodies may be numerous or scarce in cytologic preparation.[11] Bacteria tend to be less common in the later stage of malacoplakia as demonstrated clearly by Akhtar et al.[3] in a case where sequential fine needle aspiration biopsies were performed during treatment.

The cytological features of malacoplakia were first described in urinary specimens.[9] More recently, the cytopathology of malacoplakia in exfoliative specimens from the uterine cervix[6,7,10,12] and in needle aspiration biopsies from diverse sites including prostate, small intestine, colon and retroperitoneum have been described.[3]

Malacoplakia is a rare but well-recognized condition. The ages of the affected patients range from 26 to 84 years. In the few cases where cultures were done (four cases), *E. coli* was present. In the present case, both *Klebsiella* and *E. coli* were isolated. It is believed that malacoplakia results from a defective digestive capacity of the phagocytes.[1] The monocytes are able to ingest the bacteria or the cellular debris, but are unable to digest them, leading to accumulation of bacterial cells or their products as observed also in rhinoscleroma and Whipple disease,[2] which are subsequently calcified to form the Michaelis-Gutmann bodies. Abdou et al.[1] clearly demonstrated that blood monocytes in malacoplakia have decreased bactericidal activity to *E. coli.* The large lysosomal granules have low levels of cyclic GMP and poor releases of lysosomal enzyme, in some respect similar to the neutrophil abnormalities in the Chediak Highashi syndrome. The process is usually localized in a single organ system. It is sometimes associated with debilitating conditions such as use of corticosteroids[5] and tuberculosis.[8] Although there appears to be a consensus that there is a defective mechanism in the killing property of histiocytes, it is interesting to note that no septicemic process has been reported in any of the cases described in the literature, and this suggests that the bacteria are incompletely destroyed, thereby losing their pathogenic capacity to produce septicemia.

The cytological diagnosis of malacoplakia depends on the recognition of subtle changes in the histiocyte as described above. The awareness of the cytologist plays the most important role.

Atilio Baez-Giangreco, MD, FCAP
Mohammed Afzal, MD, FCAP
Consultant Pathologists
Central Laboratory and
Blood Bank
Ministry of Health
P.O. Box 60179
Riyadh 11545, Saudi Arabia
Bassam Younes, PhD
King Saud University
P.O. Box 2925
Riyadh 11461, Saudi Arabia

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Salmonella dammam: A New Serovar of Salmonella Isolated in Dammam, Saudi Arabia

To the Editor: In the Kauffman-White scheme for the classification of Salmonella,[1] more than 2000 serovars are listed and new serovars are also being reported with increasing frequency. In this letter, we describe isolation of a new serovar of Salmonella from a diarrheal stool specimen obtained from an infant in Dammam, Saudi Arabia. The strain was isolated from a 2-1/2 year old female, a Yemeni national, at the Diarrhoea Control Centre, Dammam. She had a two-day-history of diarrhea during which she passed eight to 10 loose stools per day that contained blood and mucous. She had low grade fever and was mildly dehydrated. She was treated with oral rehydration saline (ORS) only. The patient recovered after two days. Microscopic examination of stool revealed the presence of mucous and pus cells. An isolate of Salmonella was obtained after culturing the stool by using standard bacteriological technique. The strain agglutinated with Salmonella polyvalent antisera group A to S, but was negative with the available monovalent antisera group A to

G: It was sensitive to ampicillin, chloramphenicol, tetracycline, nalidixic acid and streptomycin. The strain was sent to the World Health Organization (WHO) Collaborating Centre for Reference and Research on Salmonella at the Pasteur Institute, Paris, France for biochemical characterization and serotyping.

The strain was bioptyped and serotyped according to standard methods.[2,3] It had typical biochemical profile of Salmonella subspecies. Serotyping results showed that the isolate was a new serovar of Salmonella. The strain has been registered at the WHO Collaborating Centre for Research and Reference as a new serovar of Salmonella subspecies 1 of antigenic formula 6,7:a:z6 with the name *Salmonella dammam*. *S. dammam* is probably the first serovar of Saudi Arabian origin to be included in the Kaufman-White scheme. This strain was one of the 48 nontypable Salmonella strains that were isolated in the Diarrhoea Control Centre, Dammam over a period of six months. Excepting the new serovar *S. dammam*, the remaining strains belonged to 18 different known serovars of Salmonella. This is a significantly high number for different serovar isolation in six months at a particular geographic locale. The reason for this may be the food habits of the local people. Food items are imported to Saudi Arabia from different parts of the world. Strains predominant in far off places are presumably being introduced in this country through this route.

Mohammad Imdadul Huq, PhD
Mohammad A. Al-Ghamdi, BSc
AKM Golam Kibriya, BSc
Mohammad Hussain Qadri, MD
Diarrhoea Control Centre
P.O. Box 3745
Dammam 31481, Saudi Arabia

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Mixed Gonadal Dysgenesis with Structural Anomalies of the Y Chromosome

To the Editor: In 1963, Shoval[1] reported several individuals who had one streak gonad and one dysgenetic testis. Later the term mixed (asymmetric) gonadal dysgenesis was applied to cases characterized by a unilateral testis, usually intra-abdominal and contralateral streak of gonad or agonadia, persistent müllerian duct structures and 45,X/46,XY gonosomal mosaicism.[2] Herein we report an Arab female with mixed gonadal dysgenesis, associated with different structural anomalies of the Y chromosome in 10% of the cells.

A 16-year-old Arab female was referred to the genetic clinic with proportionate short stature, primary amenorrhea and clitoromegaly. She was born to phenotypically normal, consanguineous parents. The mother was 32 and the father was 39. Pregnancy was uneventful with no history of exposure to drugs, hormones or irradiation. Comprehensive assessment by a multi-specialty team showed an intelligent masculine female. Height was 141 cm (<3rd percentile). Weight was 41 kg (<3rd percentile). Axillary hair was scanty while pubic hair showed characteristic male distribution with clitoromegaly and no labial fusion. The breasts were infantile (Tanner stage 1). The uterus was not palpable on rectal examination. Pelvic ultrasonographic examination showed a small uterus with a long, narrow cervix. Hormonal studies showed hypergonadotrophic hypogonadism, with a normal level of prolactin, high serum testosterone and low serum estradiol (Table 1). Congenital adrenal hyperplasia was excluded by normal levels of 17-OH progesterone.

Diagnostic laparoscopy followed by laparotomy were done. They showed a small infantile uterus with normal fallopian tubes and round ligaments. A pale band of tissue measuring 1.50x0.3x0.2 cm was present in the position of the right ovary. The left gonad was present in the position normally occupied by the ovary. It appeared as an infantile testis (1.6x0.9x0.5 cm) with a brown area bulging on its surface and restricted to its capsule. Bilateral gonadectomy and clitoroplasty with reconstruction of the external genitalia by excising 2 cm of the phallus shaft were done. The vagina was patent and measured 8 cm long. Postoperative estrogen therapy was started for development of feminine sexual characteristics.

Examination of 150 chromosome spreads from peripheral blood leukocyte culture using trypsin G, C and Q banding techniques showed gonosomal mosaicism with stem lines: 45,X/46,XY (53:35). Two cells had 47,XYY. Associated different structural Y anomalies were detected in 10% of the cells (Table 2).

Gonadal histopathological study showed a right gonadal streak consisting of wavy, whorled, fibrous stroma with

TABLE 1. *Hormonal profile of the patient.*

Hormone	Patient's value	(Normal value)
Lutenizing hormone	32.5 IU/L	(2.20 IU/L)
Follicular stimulating hormone	74.2 IU/L	(2-9 IU/L)
Prolactin	269 IU/L	(71-624 MIU)
Testosterone	10.2 nmol/L	(0.4-3.9 nmol/L)
Estradiol	0.1 nmol/L	(0.8-1.8 nmol/L)
17-OH Progesterone	3.8 nmol/L	(0.3-8.8 nmol/L)
DHEA-SO_4	5.4 nmol/L	(0.9-11.7 nmol/L)
S.H.B.G.	27.6 nmol/L	(20-118 nmol/L)
Growth hormone	2 nmol/L	(up to 14 nmol/L)

TABLE 2. *Cytogenetic profile of the patients.*

Karyotype.	No. of Cells	Percentage (%)
45, X	80	(53%)
46, XY	52	(35%)
47, XYY	3	(2%)
Structural abnormalities of the Y Chromosome including: ring; Yp-; Yq-; dic (Y); + mar (Y fragment)	15	(10%)
Total	150	100

occasional hilar cell nodules, prominent rete tubules and no germ cells. The left dysgenetic gonad showed tubules lined only by sertoli cells, hyperplastic Leydig cells and prominent rete tubules. Several nodules of gonadoblastoma were present at the periphery. These consist of Call Exner-like rosettes surrounded by one or more layers of granuloma cells as well as germ cells with vacuolated cytoplasm. The center of the rosettes contained hyaline material with calcified areas.

Postoperative assessment by the liaison psychiatrist showed "a pleasant cooperative female with coherent speech, euthymic mood, intact cognitive function, borderline intelligence with female gender identy and no perceptual disorder. She is worried regarding delayed menstruation and future infertility".

The present case was diagnosed as mixed gonadal dysgenesis because of the presence of unilateral testis, a contralateral streak gonad and gonosomal mosaicism with both XO and XY cell lines. If oocytes had been present, the case would have been one of lateral true hermaphroditism. It has been suggested that mixed gonadal dysgenesis may be an extreme variant of true hermaphroditism. It has been regarded to be the main form of manifestation of 45,X/46,XY mosaicism. We reported[3] a two-year, six-month-old Arab female with mixed gonadal dysgenesis.[4] She showed ambiguous external genitalia, right intra-abdominal testis, left streak gonad, bilateral müllerian derivatives, gonosomal mosaicism with multiple cell lines including structural aberrations of the Y chromosome in 36% of cells.

The streak gonads of 45,X/46,XY individuals are histologically indistinguishable from the streak gonads of individuals with 45,X gonadal dysgenesis. However, gonadoblastoma and dysgerminomas occur in about 15% to 20% of 45,X/46,XY individuals.[5] In a majority of females with gonadoblastoma, the predominant cell line is 45,X. The second cell line is 46,XY. The cell line 47,XYY has also been frequently observed.

The mechanism underlying XO/XY mosaicism is probably the result of a mitotic nondysjunction in an originally XY embryo (after the first cleavage division) causing XO/XY and XYY cell lines.

Mixed gonadal dysgenesis cases with structural anomalies of the Y chromosomes have been reported.[3,5] These include del Y (q21), ring-Y dic(Y) and isochromosome for short arm (p) or long arm (q). There is no clear correlation between the karyotype and degree of masculinization. The unstable "Y" chromosome has not been found in the father of the index cases, confirming "post-zygotic/de novo" origin of the abnormal Y chromosome.[3,6] The cause of both mitotic nondisjunction affecting the Y chromosome and associated structural damage is not well understood.

Sadika A. Al-Awadi, MD
Talaat I. Farag, DCH, MSc, DMSc
Dodderi S. Krishna Murthy, MSc, PhD
Magda H. El-Badramany, FRPsych
Magda K. Al-Azemi, MD
Kuwait Medical Genetics Centre
Maternity Hospital
P.O. Box 31121
Sulaibikat 90801, Kuwait
Mohammed Qurton, MD
Endocrinology Department
Mubarak Hospital, Kuwait

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A Saudi Health Educator Program

To the Editor: Research indicates that patient education is a vital ingredient in reducing unnecessary health care expenditures, reducing patient pain, suffering, and rehospitalization.[1] Patients who are cognizant of their condition are more likely to follow the health care regimen set forth by their care providers.[2] In the Kingdom of Saudi Arabia, patient education is often difficult since most nurses and other providers of patient education services are expatriates and unable to speak the appropriate Arabic dialect fluently enough to adequately educate their patients:

We would like to describe a pilot program designed at King Faisal Specialist Hospital and Research Centre (KFSH&RC) to improve the quality of patient education.

To our knowledge, there has been no other program of its kind in the Middle East. The Saudi Health Educator Program arose out of certain positive outcomes of our Medical Clinical Translator Program. The translators had demonstrated that they were ready, willing and able to take on more complex assignments and to contribute more to health care delivery. It was also felt that the role of health educator was a positive step in the process of Saudization. Young Saudi nationals could develop skills and further their own professional growth, and ultimately have a positive impact on the health care system in the Kingdom.

A 12 month program was developed that included a science base. Emphasis was on anatomy and physiology, pathophysiology, basic nutrition and medical terminology as well as teaching/learning theories and practice. A variety of specialty courses provided background information about health promotion, the health care system, human development, and the disease processes treated at KFSH&RC. Clinical experience and independent study time were also important components of the program. The goal of the Saudi Health Educator Program was to develop patient educators who could discuss health issues with the Saudi population in their dialect and with full respect for their culture. Today, the health educators facilitate effective communication and function as part of the health care team alongside the physician, nurse, patient and the patient's family.

Prerequisites for joining the program were Saudi nationality, a bachelor's degree, preferably in a science or in education and fluency in written and spoken English. The program began in September 1992 (Rabi Al Awal 1413H). In the first five months of the program, the emphasis was totally in the classroom, ensuring that the students acquire adequate theoretical knowledge and background. At the sixth month, a clinical lab was integrated into the classroom routine. This consisted of role playing of patient teaching situations. The student had the opportunity, over time, to play the roles of patient, sitter, nurse and health educator. The students were divided into two groups. Scenarios were given to each group of students, which were to be used as guidelines to teach the patient in each given situation. The students were responsible for enlarging on the information given in the scenario, while ensuring that the information given to the patient was logical for the patient's problem and that the information given was not beyond the scope of the health educator. At first, the students found the role playing quite difficult, since this was a new experience for most of them. The role playing was necessary to give the students basic skills and confidence before coming in contact with patients. Mistakes, which could have been major problems had they been made in the clinical situation with real patients, were corrected, and the simulations served as excellent learning experiences. The role playing activities were also an excellent tool to encourage team building, which would be important in the clinical situation. The students began the clinical activities in the eighth month, with the ninth through 12th months being totally clinically focused, except for a major teaching project that each student developed.

On 28 September 1993, the Saudi Health Educator Program graduated seven students who deliver patient education services in several forms. The most basic is translation for the nursing staff. The health educators also independently teach preop and postop instructions, patient-controlled analgesia, tracheostomy care, pre and post liver biopsy instructions and chemotherapy instructions, as well as other patient education as needed. The health educators accompany nurses when they present information to patients in order to see/hear how that information is communicated. Depending upon the complexity of the information, the health educator may accompany the nurse only once, or many times. The health educator is responsible for looking up information in reference books on the unit before teaching sessions. This assures both the nurse and the health educator that only appropriate information will be given to patients. The type of information an educator may present is determined by the type of unit to which the educator is assigned and the educator's experience. The health educators will have the opportunity to increase knowledge and repertoire of independently taught topics as patients with new and different diseases appear and as new procedures are done on their assigned units. Communicating accurate information to the patient about what is/will be happening to him/her in the complexities of the hospital system is also an important part of the health educator's role.

In the beginning, the idea of health educator was not received well in all quarters. Nurses tend to hold patient education near and dear and were not always enthusiastic about non-nurses functioning in this capacity. However, the eagerness and ability of the health educators soon won those over who were not so positive in the beginning. The health educators feel themselves very fortunate to work on the seven units. Communication between patients and staff has been enhanced. The patients will reveal vital information to the health educator that they would not, or could not, to the nurse. The time savings for both the nurse and the ward clerks who were being used as translators has been tremendous. The patients have responded in a very positive way to the health educators. They are very pleased to have someone who speaks their language and understands their culture to be able to speak with about the many complexities of the health care system.

The year-long program held many challenges, as well as learning and growth opportunities, for both students and instructors. Transcultural education as a field has not been studied extensively. As instructors from North America, we were not sure of the teaching techniques that would be most appropriate for our Saudi students. In the end, our techniques were basically the same as we used in our home country; however, we were careful to be culturally congruent in our educational practices, keeping in mind Leininger's theory of Culture Care Diversity and Universality.[3] Examples of cultural congruency included making sure the room was set up in such a manner that males and females would be segregated, making the scheduled leave times during the Holy Month of Ramadan and during Haj, and in segregating males and females and providing privacy for laboratory activities such as testing of deep tendon reflexes, blood pressure readings and cardiopulmonary resuscitation classes. Throughout the program, the instructors felt we were learning as much about Saudi culture as our students were learning about the health sciences.

Cassandra Barber, RN, MS, CRRN
Julia Bronner, RN, MS, CNS
King Faisal Specialist Hospital
and Research Centre
Nursing Education and Research
MBC-63
P.O. Box 3354
Riyadh 11211, Saudi Arabia

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Serum Fructosamine Levels in Thyroid Disease

To the Editor: Serum fructosamine concentration was measured in 28 normal controls, 47 hyperthyroid and 68 hypothyroid adult, non-diabetic subjects. The mean fructosamine concentration in hyperthyroid patients (242 μmol ± 58) was significantly lower than in hypothyroid (284 μmol ± 56), and euthyroid (271 μmol ± 28) individuals ($P<0.001$ and <0.01 respectively). It is suggested that serum fructosamine concentration, as an index of glycemic control in diabetics with thyroid disease, must be interpreted with caution.

Serum fructosamine concentration, which reflects glycosylated protein levels, particularly albumin, has been proposed as a reliable index of intermediate term (1 to 3 weeks) metabolic control of diabetes mellitus.[1] It has been shown that hypothyroidism is associated with an increase and hyperthyroidism with a decrease of serum fructosamine values.[2]

Blood was collected from normal, hypothyroid and hyperthyroid nondiabetic subjects. Serum was separated as soon as possible and immediately frozen until analyzed for free thyroxine (FT4), thyroid stimulating hormone (TSH). fructosamine and albumin. Serum concentrations of FT4 and TSH were measured by nonisotopic immunoassay methods using the Amerlite system (Amersham International Plc, Amersham, U.K.). Serum fructosamine was measured by an automated method on Hitachi 717 analyzer using Boehringer reagents. Serum albumin was measured by a standard procedure on Hitachi 717 analyzer. Data were statistically analyzed using the impaired Student's t-test and differences were considered significant whenever the P value was <0.05.

TABLE: *FT4, TSH and fructosamine concentrations in the three groups of subjects studied.*

	Age (mean & range)	FT4 (pmol/L) (mean & SD)	TSH (mIU/L) (mean & SD)	Fructosamine (μmol/L) (mean & SD)
Normal controls (n=28)	43(18-74)	16.32(±2.62)	1.51(±1.51)	271(±28)
M 10				
F 18				
Hyperthyroid (n=47)	41(14-79)	43.51(±23.38)	0.37(±0.7)	244(±58)*
M 17				
F 30				
Hypothyroid (n=68)	47(16-83)	8.39(±4.73)	50.32(±48.47)	284(±56)+
M 25				
F 43				

*=significantly different ($P<0.001$) from controls; +=significantly different ($P<0.01$) from controls; SD=standard deviation.

The serum fructosamine levels in hyper and hypothyroidism were significantly lower or higher than in the normal controls (244 ± 58, 284 ± 56, 271 ± 28 μmol/L) ($P<0.001$ and <0.01) respectively (table). However, no correlation was found between serum fructosamine values and FT4, TSH or albumin levels (data not shown).

The present study confirms that thyroid disease is associated with abnormal fructosamine values when compared with those in normal subjects. The mechanism responsible for these variations in serum fructosamine concentration is still unknown. A possible explanation for these changes might be in a reduction of plasma protein turnover in hyperthyroidism.[3] Similar results were reported by Lloyd and Marples.[2]

However, Cirillo et al.[4] found no significant difference in serum fructosamine concentration between hyperthyroid and normal controls, but confirmed the difference in the hypothyroid group.

In conclusion, we suggest that serum fructosamine concentration in patients with thyroid disease should be interpreted with caution. An increase of fructosamine level does not necessarily reflect the state of metabolic control of diabetes mellitus, but can be ascribed to hypothyroidism in the absence of hyperglycemia.

Tarif H. Zawawi, FRCP(I)
Elsadig M. Abdelwahab, FRCPath
King Khalid National Guard Hospital
P.O. Box 9515
Jeddah 21423, Saudi Arabia
Khalid Marzouki, Facharzt
Zuhair Marzouki, PhD
King Abdulaziz University Hospital
Jeddah 21423, Saudi Arabia

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Book Reviews

Histology

by Alan Stevens, James S. Lowe and two contributors
Gower Medical Publishing Limited, New York, NY, USA
1st Edition, 1991
US $69.95
ISBN: 0-56375-571-8

It is a pleasure to receive this book for review. The text is well written, easy to read and understand, complemented by high quality diagram, photomicrograph and ultrastructural pictures.

It consists of 19 chapters that give good, precise coverage of human histology. The first two chapters provide significant and basic cellular structure to understand and study histology. The remaining chapters provide comprehensive and extensive discussion of various systems. It provides both practical histology and clinical implications with a good table and beautiful illustrations, facilitating better understanding of the background of certain clinical subjects.

One point is that this text does not provide a separate chapter on the theory of histotechnology, special methods and types of fixatives used to attain better stains, i.e., routine stain or that used for immunohistochemistry or ultrastructural studies.

Lastly, I have no hesitation to recommend this book to medical students as well as to junior residents in pathology.

Mohammed O. Al-Sohaibani, MD
Associate Professor of Pathology
College of Medicine
King Saud University
P.O. Box 2925 (32)
Riyadh 11461, Saudi Arabia

Brain Blood Flow in Neurology and Psychiatry

by P. J. Ell and D. C. Costa
Churchill Livingston Medical Division
of Longman Group UK Limited,
London, England
First Edition, 1991
US $45
ISBN: 0-443-04282-9

The decade of the brain (1990 to 2000) was heralded by two decades of exponential progress in the techniques for imaging of intracranial structures. Displaced by CT and MRI, the radionuclide brain scan lost the position it held in the sixties as the only noninvasive method for investigating intracranial pathology. Radioisotopes should have a better role than depiction of static anatomical structures. As dynamic tracers, radiopharmaceuticals are better suited for functional studies such as cerebral bloodflow, substrate utilization, and receptor localization. The latter two are the subject of investigation by PET scanning, whose academic nature and prohibitive cost have prevented it from entering into daily clinical application.

Spect (or spet as abbreviated in the book) has been proven reliable in investigating cerebral bloodflow at a reasonable cost. The technique, however, is underutilized. This is partly due to lack of familiarity among radiologists and clinicians with what it can offer.

This book is intended as a primer for clinicians and radiologists to introduce the technique and its applications. It is concise, produced in a pocket size, and written in a lucid and quite readable format. The part allotted for discussion of the pharmaceutical is limited to the necessary, and avoids boring esoteric discussion. About two-fifths of the book is devoted to case reports, covering the spectrum of situations in which technetium^{99} HMPAO spect was useful. Migraine, epilepsy, dementia, cerebral vascular disease and Parkinson disease are well covered. There are plenty of high quality color images that make the book attractive. Although no claim is made for the cases, so as to be exhaustive, it would have been more useful if it included illustrations about different types of dementia such as progressive supranuclear palsy, Korsakoff syndrome and Creutzfeld-Jakob disease, to demonstrate how their flow pattern may be at variance with that of Alzheimer disease.

In general, the book is a valuable addition to the libraries of physicians interested in nuclear medicine or neurosciences.

M. Zuheir Al-Kawi, MD, FAAN
Head, Section of Neurology
Department of Medicine (MBC-46)
King Faisal Specialist Hospital
and Research Centre
P.O. Box 3354
Riyadh 11211, Saudi Arabia

Atlas of Transesophageal Echocardiography in Clinical Practice

by George Sutherland, Joseph Roelandt, Alan Fraser, Robert Anderson
Gower Medical Publishing Limited, New York, NY, USA
1st Edition, 1991
US $170
ISBN: 0-397-44640-3

This book is presented in 15 chapters that are written by experienced contributors in the field of echocardiography in The Netherlands and the United Kingdom.

The introductory chapter briefly mentions the objectives of the book and the experience of the editors in the techniques of transesophageal echocardiography.

A subsequent chapter covers the history of transesophageal echocardiography, its application in cardiology, the progress in the development of the technique and the characteristics of the transesophageal systems and its technical features. This chapter is followed by a detailed normal examination with emphasis on the various imaging planes and the anatomical features depicted by the technique. Other chapters deal with the versatility of the transesophageal technique in depicting various pathoanatomy in the atria and the atrioventricular valves as well as detection of the normal pulmonary venous flow and the significant change that occurs in various cardiac abnormalities.

Prosthetic valve evaluation and endocarditis in both native and prosthetic valves are also discussed in greater detail in two chapters with emphasis on the advantages and limitations of the transesophageal techniques.

The advantages of the technique in detecting diseases of the aortic valve, the left ventricular outflow tract and the thoracic aorta including dissection are well covered in two other chapters.

The technique application in ischemic heart disease and its utility in detecting myocardial ischemia, complications of myocardial infarction and abnormalities of the coronary arteries also occupy one chapter.

The major impact of the transesophageal technique has been in its usefulness in the operating room where it is used for intraoperative evaluation of left ventricular function and assessment of surgical cardiac repair of both acquired and congenital heart diseases. Two chapters are devoted to these vital issues.

The last two chapters cover in detail the application of the transesophageal technique in congenital heart disease in children, adolescents and adults with notation of the merits and demerits of the technique.

The book is well illustrated with high quality echocardiographic and Doppler color flow images. These are accompanied frequently with schematic diagrams, anatomic sections, and occasionally magnetic resonance images. It is well written and easy to understand.

The book, however, deals mainly with the technique of single plane transesophageal echocardiography with occasional reference to the biplane technique. The latter technique is now widely used and has established definite superiority. In fact, now the omniplane (multiplane) technique has been born.

These new technologies are currently replacing the old technique of single plane transesophageal echocardiography, which is the major issue of this book.

This textbook is intended primarily for those who are learning the technique of transesophageal echocardiography. The book is of great help to cardiologists as well as cardiac surgeons and anesthetists who are keen to apply the technique in the operating room.

Mohamed T. Idris, MD
Consultant Cardiologist
Riyadh Armed Forces Hospital
P.O. Box 7897
Riyadh 11159, Saudi Arabia

Announcements

The *Annals of Saudi Medicine* is pleased to publish announcements of educational opportunities of interest to its readers. For adequate publication layout time for publicity, notices of postgraduate schedules, courses, meetings, and lectures must be received at least **six months prior** to the date of occurrence. Please send relevant information to *Annals of Saudi Medicine*, Publications Office (MBC-36), Academic Affairs & Postgraduate Education, King Faisal Specialist Hospital & Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia. Tel: 464-7272 extensions 1815/1816; Fax: (01) 442-7237.

King Faisal Hospital & Research Centre Academic Calendar for 1414H/1993-1994

King Faisal Specialist Hospital & Research Centre has scheduled the following Academic Calendar for 1994-1995/1415H:

United States Medical Licensing Examination (USMLE) Step 2	31 August-1 September 1994 (24-25 Rabi Al-Awal 1415)
United States Medical Licensing Examination (USMLE) Step 1	22-23 September 1994 (17-18 Rabi Al-Thani 1415)
Growth Disorders in Children	13-15 November 1994 (10-12 Jumada Al-Thani 1415)
Second International Conference on AIDS - Saudi Arabia	28-20 November 1994 (25-27 Jumada Al-Thani 1415)
Recent Advances in the Diagnosis and Management of Allergic Diseases	10-11 January 1995 (9-10 Shaban 1415)
International Symposium on Inborn Errors of Metabolism	24-25 January 1995 (23-24 Shaban 1415)
United States Medical Licensing Examination (USMLE) Step 2	1-2 March 1995 (30 Ramadan-1 Shawwal 1415)
Nursing Management: Strategies for the Future	14-15 March 1995 (13-14 Shawwal 1415)
Advances in the Management of Head and Neck Oncology	28-30 March 1995 (27-29 Shawwal 1415)
Neuromotor Control and Rehabilitation of the Neurologically Impaired Patient	12-13 April 1995 (12-13 Dhu Al-Qa'da 1415)
International Symposium on Pediatric Gastroenterology, Hepatology and Nutrition	23-24 April 1995 (23-24 Dhu Al-Qa'da 1415)
Intensive Course in Microsurgery	17-24 May 1995 (18-25 Dhu Al-Hijjah 1415)
Radiology Centennial Seminar	24-25 May 1995 (25-26 Dhu Al-Hijjah 1415)

For further information, contact: Academic Affairs & Postgraduate Education (MBC-36), King Faisal Specialist Hospital & Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia; Tel: (01) 442-7238, or Fax: (01) 442-7237.

King Faisal Specialist Hospital & Research Centre Postgraduate Training Programs

King Faisal Specialist Hospital & Research Centre is pleased to invite applications for the following full-time postgraduate training programs:

1. Arab Board residency training in the specialties of internal medicine, obstetrics/gynecology, pediatrics, and surgery.
2. Five-year pathology residency training program affiliated with King Saud University, the Royal College of Pathologists of Australasia and the Royal College of Pathologists of Great Britain.
3. Fellowships are offered in the following areas: Cardiovascular Diseases; cardiology, pediatric cardiology, thoracic and cardiovascular surgery. Oncology; hematology, medical oncology, and pediatric hematology-oncology. Medicine; endocrinology, gastroenterology, infectious diseases, nephrology, pulmonology, critical care, and rheumatology. Pediatrics; allergy and clinical immunology, neonatal/perinatal medicine, gastroenterology and hepatology, infectious diseases, nephrology, neurology, genetics, metabolic diseases, and endocrinology.

For further information, contact: Director, Academic Affairs & Postgraduate Education (MBC-36), King Faisal Specialist Hospital & Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia; Tel: (01) 442-7214, or Fax: (01) 442-7237.

King Saud University Fellowship in Pathology

King Saud University announces the inception of a five-year joint fellowship training program in pathology. The training will be held at King Khalid University Hospital, King Faisal Specialist Hospital & Research Centre, Riyadh Armed Forces Hospital, King Fahad National Guard Hospital, and is a full-time fellowship training program. Application is open to interested and suitably qualified residents from all over the Kingdom of Saudi Arabia. To be eligible, applicants will meet the following criteria:

1. Doctors who hold an MB, BS from King Saud University or equivalent degree.
2. Doctors who have completed their internship in a recognized hospital.
3. Undergone successful completion of a selection examination and personal interview.
4. Applicants from other institutions should submit a letter from his/her employer that he/she will be sponsored during the entire period of training.

Application forms and inquiries should be forwarded to the Director of the Residency Training Program, College of Medicine, King Saud University, P.O. Box 2925, Riyadh 11461, Saudi Arabia, or contact the Residency Board secretary at Tel: 467-1551/1556/1564, or Fax: 481-1853.

VII International Congress of Pediatric Dermatology, Buenos Aires, Argentina, 1994

The VII International Congress of Pediatric Dermatology will be held from 26 September to 1 October 1994(21 to 26 Rabi Al-Thani 1415H) in Buenos Aires, Argentina.

Topics to be addressed are intended to cover atopic dermatitis, nutritional disorders, AIDS, and genodermatoses.

For further information, contact: Dr. Adrian M. Pierini, President, VII International Congress of Pediatric Dermatology, Arenales 1446 Ap. 1B, (1061) Buenos Aires, Argentina. Tel: (54.1) 814-4068, or Fax: (54.1) 812-9255.

Fourth International Course on Magnetic Resonance Imaging, Riyadh Armed Forces Hospital, 1994

The Fourth International Course on Magnetic Resonance Imaging (MRI) will be held from 2 to 5 October 1994(27 to 30 Rabi Al-Thani 1414H) by the Departments of Radiology, Medical Physics and Medical Studies of the Riyadh Armed Forces Hospital.

The course will provide an overview of MR Technology and basic principles, current and future applications of MR in the whole body. Current and potential applications of MR in the spectroscopy will also be discussed. Small group workshops on Basic Physics, Neurological Applications, Musculoskeletal, and Genitourinary Systems will be provided for all participants.

For further information, contact: Department of Medical Studies, Riyadh Armed Forces Hospital, P.O. Box 7897, Riyadh 11159, Saudi Arabia. Tel: (966) (01) 477-7714, extensions 2289/2269, or Fax: (966) (01) 477-7194/477-9168.

Fourth Workshop on Medical Writing and Editing, Ministry of Health, Singapore, School of Postgraduate Medical Studies and the Faculty of Medicine, National University of Singapore, 1994

The Fourth Workshop on Medical Writing and Editing, sponsored by the Ministry of Health, Singapore, School of Postgraduate Medical Studies and the Faculty of Medicine, National University of Singapore, will be held from 7 to 9 October 1994(2 to 4 Jumada Al-Awal 1415H).

The teaching faculty will comprise the Editors of the prestigious *Annals of Internal Medicine,* Drs. Robert and Suzanne Fletcher.

The three-day program has also been designed to provide a forum for medical writers and editors to learn from the teaching faculty as well as from one another's experience. The program will include lectures and small group workshops.

The Organizing Committee plans to formalize the APSEA(Asia-Pacific Scientific Editors Association) during this workshop.

The first day of the Workshop will be directed at young contributors, providing them with hands-on experience in the art of writing. The second and third day will be devoted to an exchange of ideas and transfer of skills between the visiting faculty and the local and regional editorial boards, and the formation of the APSEA.

For further information, contact: The Editorial Assistant, Fourth Workshop on Medical Writing and Editing, Annals, Academy of Medicine, Singapore, 16 College Road #01-01, College of Medicine Building, Singapore 0316. Tel: 224-5166, or Fax: 225-5155.

Fifth Advanced Medicine Symposium & Workshop on Tuberculosis Control, Riyadh Armed Forces Hospital Department of Medicine & Department of Postgraduate & Academic Affairs, 1994

The Fifth Advanced Medicine Symposium will be held from 16 to 18 October 1994(11 to 13 Jumada Al-Awal 1415H) at Riyadh Armed Forces Hospital Department of Medicine & Department of Postgraduate & Academic Affairs, Riyadh, Saudi Arabia.

For further information, contact: Department of Postgraduate & Academic Affairs, Riyadh Armed Forces Hospital, P.O. Box 7897, Riyadh 11159, Saudi Arabia. Tel: (966)(01)477-7714, extensions 4937/4936/4935/4934, or Fax: (966)(01)478-1017.

International Symposium on Advances in Minimal Invasive Surgery, Riyadh Armed Forces Hospital, 1994

The International Symposium on Advances in Minimal Invasive Surgery will be held from 1 to 3 November 1994(27 to 29 Jumada Al-Awal 1415H) at Riyadh Armed Forces Hospital,Riyadh, Saudi Arabia.

A series of keynote lectures will be presented by invited international speakers.

For further information, contact: The Chairman, Organizing Committee, International Symposium on Advances in Minimal Invasive Surgery, Department of Postgraduate & Academic Affairs. Riyadh Armed Forces Hospital, P.O. Box 7897, Riyadh 11159, Saudi Arabia. Tel:(966)(01)477-7714, or Fax:(966)(01)478-4057.

Symposium on Growth Disorders in Children, Academic Affairs & Postgraduate Education, 1994

A Symposium on Growth Disorders in Children will be held from 13 to 15 November 1994(10 to 12 Jumada Al-Thani 1415H)in the King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia.

Overseas participants must obtain visa application forms provided by Academic Affairs & Postgraduate Education three months in advance.

For further information, contact: Academic Affairs & Postgraduate Education (MBC-36), King Faisal Specialist Hospital & Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia. Tel: (966)(01)442-7238, or Fax: (966)(01)442-7237.

International Symposium on Recent Advances in Arthroscopic Surgery, Riyadh Armed Forces Hospital, Department of Postgraduate & Academic Affairs, 1994

The International Symposium on Recent Advances in Arthroscopic Surgery will be held from 16 to 17 November 1994(13 to 14 Jumada Al-Thani 1415H) at Riyadh Armed Forces Hospital, Riyadh, Saudi Arabia.

For further information, contact: Dr. Husham A. Hasan, FRCS, Symposium Organizer, Department of Postgraduate & Academic Affairs, Riyadh Armed Forces Hospital, P.O. Box 7897, Riyadh 11159, Saudi Arabia. Tel: (966)(01)477-7714, or Fax: (966)(01)478-4057.

The "Second International Conference on AIDS-Saudi Arabia", Department of Medicine and Department of Academic Affairs & Postgraduate Education, 1994

The "Second International Conference on AIDS-Saudi Arabia" will be held from 29 to 30 November 1994(26 to 27 Jumada Al-Thani 1415H) by the Department of Medicine at the Cultural Palace in the Diplomatic Quarter, Riyadh, Saudi Arabia.

Overseas participants must obtain visa application forms provided by Academic Affairs & Postgraduate Education by 29 August 1994.

For further information, contact: Academic Affairs & Postgraduate Education (MBC-36), King Faisal Specialist Hospital & Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia. Tel:(966)(01)442-7238, or Fax: (966)(01)442-7237, or contact the Department of Medicine (MBC-46).Tel: (966)(01)442-7771, or Fax: (066)(01)442-7499.

6th Scientific Session, Saudi Heart Association, 1995

The Saudi Heart Association will hold its 6th Scientific Session from 24 to 26 January 1995(22 to 24 Rajab 1415H) in Jeddah, Saudi Arabia. Invited guest faculty include world-recognized cardiologists and cardiac surgeons.

Abstracts of papers for presentation are being accepted. Original work related to all aspects of cardiovascular diseases will be considered, with particular emphasis on:(1) coronary artery disease; (2) valvular heart disease; (3) pericardial disease; (4) interventional cardiology; (5) noninvasive cardiology; (6) infective endocarditis; (7) cardiac surgery; (8) pediatric cardiology; (9) cardiac anesthesia; and (10) congestive heart failure.

Abstracts submitted for consideration must be received by the Saudi Heart Association no later than 1 September 1994(25 Rabi Al-Awal 1415H). . Interested overseas participants must obtain entry visa information from the Saudi Embassy or consulate office in their own country.

For further information, contact: The Saudi Heart Association, College of Medicine, King Saud University, P.O. Box 2925, Riyadh 11461, Saudi Arabia. Tel: (966)(01)467-1554, or Fax: (966)(01)481-1853 or 467-1379.

5th World Congress on Clinical Nutrition, Hangzhou, China, 1995

The 5th World Congress on Clinical Nutrition will be held from 7 to 11 October 1995 in Hangzhou, China.

The aim of this Congress is to popularize nutrition training and practice in medical schools, hospitals and private practice. This is an extraordinary opportunity for healthcare employees, especially physicians and dietitians in China and worldwide, to meet the nutrition experts.

For further information, contact: Prof. Zhu Shoumin, Department of Nutrition, Zhejiang Medical University, Hangzhou, Zhejiang-310031, China. Tel: (571)722700, or Fax: (571)771571.

العيوب غير القلبية لدى الأطفال المصابين بداء القلب الخلقي

أجرينا خلال تسعة وثلاثين (٣٩) شهراً، دراسة على العيوب غير القلبية لدى ٣٢٠ طفلاً سعودياً حضروا لأنهم يعانون من داء القلب الخلقي. تم اكتشـاف تسعـين عيبـاً غير خلقي لدى ٨٠ طفلاً (٢٥٪) من بين الأطفال الثلاثمائة والعشرين. شكلت المتلازمات المعروفة ٤٩ عيباً (٥٤٪) من العيوب التسعين غير القلبية، وكان ٣٢ عيباً من عيوب المتلازمات التسعة والأربعين (٦٥٪) ناجماً عن الإصابة بمتلازمة داون وحدها. بعد عيوب المتلازمات، جاءت العيوب الهيكلية العضلية (٢٤,٥٪) والعيوب العصبية (٩٪) وعيوب الجهاز الهضمي (٨٪). وكما هو متوقع، ظهر ارتباط بين متلازمة داون والعيوب في الحاجز القلبي. كان ٢٨ (٨٧,٥٪) من المرضى الإثنين والثلاثين الذين يعانون من هذه المتلازمة مصابين بنوع من عيوب الحاجز القلبي، وحدثت ١٦ حالة من حالات العيب في القناة الأذينية البطينية لدى مرضى تثلث الصبغي ـ ٢١. عموماً، اعتبرت العيوب غير القلبية متوسطة الشدة أو شديدة لدى ٦٧ (٨٤٪) من المرضى الثمانين المصابين. وفي الحقيقة، كان ٤٨ مريضاً (٦٠٪) من المرضى الثمانين (أو ١٥٪ من المجموعة الأصلية المكونة من ٣٢٠ مريضاً) يعانون من درجات متفاوتة من التخلف العقلي. تؤكد نتائج هذه الدراسة الارتباط الواضح تماماً بين تثلث الصبغي ـ ٢١ والتشوه القلبي، كما تؤكد على الحاجة لإجراء بحوث على هذه العيوب لدى أي طفل يبدو عليه النمط الظاهري لمتلازمة داون. وتفترض نتائج هذه الدراسة أيضاً أن نسبة الإصابة بعيب خطير غير قلبي عالية نسبياً لدى الأطفال الذين يعانون من داء القلب الخلقي. ومن الضروري إجراء دراسات شاملة في المملكة لدراسة العيوب عند الولادة، وإذا ما أعطت هذه الدراسات نتائج مماثلة لنتائج هذه الدراسة، فيجب النظر في وضع استراتيجيات مناسبة للوقاية.

وضع السرطان في مستشفى القوات المسلحة في الرياض

يختلف نمط الوقوع ومعدلات الوفاة الناجمة عن الأمراض الخبيثة تبعاً للجنس والعمر والعرق والموقع الجغرافي. وتختلف نسبة الوقوع في الدول المختلفة والنامية مع التغير الملحوظ الذي يحدث في كل عقد. أكدت مراجعة أول ٥٠٠٠ حالة مرض خبيث مثبت نسجياً والتي شوهدت في قسم الأورام في مستشفى القوات المسلحة في الرياض اختلاف نمطها عن الأمراض الخبيثة التي شوهدت في مستشفيات أخرى. عموماً، كانت حالات سرطان الجهاز الهضمي هي المجموعة الأكثر تواردا، إذ بلغت نسبتها ١٨٪ تقريباً، مع نسبة وقوع مرتفعة لسرطان الكبد وسرطان المريء. كان سرطان القولون والمستقيم، كما هو متوقع، أقل تواردا مما هو عليه في الغرب، ويفترض أن ذلك يعود إلى طبيعة النظام الغذائي الخاص بالمنطقة. كانت الأورام اللمفية في المرتبة الثانية من حيث التوارد، إذ بلغت نسبتها ١٣٪، وكانت نسبة الأورام اللمفية غير الهدجكينية إلى داء هدجكن ١:٢,٥. كانت المتغيرات النسيجية سيئة الإنذار، في كلا المجموعتين، أكثر تواردا مما هي عليه في الغرب. كان سرطان الثدي هو الأكثر تواردا لدى الإناث، إذ بلغت نسبته ٢٤٪ من جميع حالات السرطات لديهن، هذا بالرغم من ندرة عوامل الخطورة التقليدية مثل العائط والخروس المسنة وتأخر الإياس وكثرة الدهنيات في الغذاء. كان ثلثا المريضات المصابات بسرطان الثدي في سن ما قبل الإياس. اشتملت الأمراض الخبيثة الأخرى التي تمت مواجهتها بتوارد أكثر مما هي عليه في الدول المتخلفة على سرطانة خلايا الكبد، وسرطان البلعوم الأنفي. وقد يعزى هذا التوارد المرتفع نسبياً إلى ارتفاع نسبة الوقوع لالتهاب الكبد الحموي (الفيروسي) والإلتهابات بفيروس إيستين ـ بار على التوالي. ويفترض أن التوارد المرتفع نسبياً لسرطان جوف الفم يمكن أن يكون ناجماً عن مضغ القات والشمة. كان التوارد النسبي لسرطان الدرقية أعلى من ٥٪، مع غلبته بصورة مرتفعة لدى الإناث. لم يتم تحديد عوامل واضحة لسبب المرض. كان التوارد النسبي للسرطان القصبي المنشأ منخفضاً، إذ بلغ ٥٪. ومن المرجح أن ذلك سيزيد مع الزيادة المطردة في عادة تدخين السجائر. كان سرطان الجلد، من ناحية أخرى، منخفضاً، ويفترض أن ذلك يعود إلى اللباس التقليدي الذي يغطي كامل الجسم والرأس.

المدونات الطبية السعودية ١٩٩٤م، ١٤ (٣): ١٨٧ ـ ١٩٤.

سرطان المعدة في جنوب المملكة العربية السعودية

تم تشخيص ما مجموعه ٨٤ حالة من السرطان الأولي في المعدة في مختبر التشريح المرضي النسيجي بمستشفى عسير المركزي خلال فترة خمس سنوات (١٩٨٧م إلى ١٩٩١م). كان ٧٢ مريضاً (٨٦٪) من السعوديين و١٢ مريضاً (١٤٪) من غير السعوديين. كان متوسط العمر للمرضى المشمولين في هذه الدراسة ٦٠ عاماً، ومدى الأعمار ٢٢ إلى ٨٥ عاماً، ونسبة الذكور: الإناث ٤,٦:١. ظهرت السرطانة الغدية المعوية لدى ٦٣ مريضاً (٧٥٪) تلاها الأورام اللمفاوية الخبيثة لدى ١٢ مريضاً (١٤٪) والسرطانة الغدية المنتشرة لدى ٩ مرضى (١١٪). كان غار المعدة أكثر الأماكن تأثراً (٤٧٪) تلاه جسم المعدة (٢٧٪) والفؤاد (١٤٪) والقاع (١٢٪). وتعرض هذه الدراسة مقارنة بين النتائج التي توصلنا إليها وتقارير مشابهة من مناطق أخرى من المملكة العربية السعودية وبلدان أخرى.

المدونات الطبية السعودية ١٩٩٤، ١٤ (٣): ١٩٥ـ١٩٧.

الغرن الكيسي الورقي الخبيث
مراجعة للخبرة السريرية في مستشفى الملك فيصل التخصصي ومركز الأبحاث

أحيلت ١٢ مريضة مصابة بغرن كيسي ورقي في الثدي إلى مستشفى الملك فيصل التخصصي ومركز الأبحاث في الفترة من ١٩٨٠م إلى ١٩٩٠م، ومثلن نسبة ٠,٨٪ من مريضات سرطان الثدي اللواتي شوهدن خلال هذه الفترة. كان العمر المتوسط ٤٥ سنة (المدى ١٦ إلى ٦٥ سنة) وكانت سبع مريضات (٨٥٪) قبل سن الإياس. راجعت جميع المريضات المستشفى بسبب كتلة الثدي التي كان حجمها يزيد عن ١٠سم لدى ٥٨٪ منهن. كانت المدة المتوسطة للأعراض ١٥ شهراً (المدى من ٢ إلى ١٧٤). لم تشاهد عقد لمفية إبطية ولا انتقالات بعيدة لدى المراجعة. كانت الجراحة هي أساس العلاج الأولي (استئصال واسع النطاق لدى ثلاث واستئصال الثدي لدى تسع). تلقت مريضتان معالجة كيميائية مساعدة ومعالجة موضعية بالأشعة. كان الورم خبيثاً لدى جميع المريضات طبقاً للفحص النسيجي. ومن بين الأورام الأربعة التي أجريت لها مقايسة للمستقبلات الهرمونية كان واحد منها إيجابياً لمستقبلات الإستروجين والبروجستيرون. بعد متابعة متوسط مدتها ١٧ شهراً (المدى من ٢ إلى ٧٧) انتكست أربع مريضات، وتوفيت واحدة بعد ١٩ شهراً، وكانت نسبة البقيا لمدة خمس سنوات ٨٣٪. تشير هذه البيانات المحدودة إلى أن الغرن الكيسي الورقي الخبيث هو كيان سريري باثولوجي متميز من سرطان الثدي الأنثوي، وله تاريخ طبيعي مختلف عن سرطانة الثدي. تماثل نتائج البقيا التي حصلنا عليها الخبرات المنشورة في المراجع العلمية.

المدونات الطبية السعودية ١٩٩٤، ١٤ (٣): ١٩٨ـ٢٠٠.

زيادة في ابتداء السكتة الإقفارية في الصباح الباكر

أجريت دراسة على ٥٢٥ مريضاً متتالياً تتراوح أعمارهم بين ٣٦ و٨٦ عاماً لتحديد ما إذا كان التفاوت النهاري يؤثر على ابتداء السكتة الإقفارية الحادة. كان هناك تفاوت نهاري واضح (أقل من ٠,٠١ درجة الاحتمال P ، ٠,١٩ ـ Dmax) مع ذروة ملوحظة (أقل من ٠,٠٠١ درجة الاحتمال P ، ٤,٩٦ ـ t) بين الساعة الرابعة والسادسة صباحاً. وكانت السكتات أكثر حدوثاً خلال الساعتين التاليتين للإستيقاظ منها في أي وقت آخر من النهار. كان زمن الذروة للسكتة الإقفارية في دراستنا أبكر مما ورد في التقارير

السابقة بساعتين تقريباً، ربما بسبب اختلاف أوقات الاستيقاظ لدى المرضى الذين أجريت عليهم الدراسات. نخلص إلى القول بأن زمن الاستيقاظ هو الذي يؤثر على التوزيع اليوماوي وليس التفاوت النهاري بحد ذاته.
المدونات الطبية السعودية ١٩٩٤م، ١٤ (٣): ٢٠١_٢٠٢.

قصور تنفسي شديد مرافق للإصابة بجراثيم اللجيونيلا الرئوية

أدخل أربعة مرضى إلى وحدة العناية المركزة بمستشفى الملك خالد الجامعي بسبب إصابتهم بقصور تنفسي شديد. أظهرت الاستقصاءات الشاملة وجود دليل مصلي على التهاب جرثومي بجراثيم اللجيونيلا. استلزمت حالة ثلاثة مرضى وضعهم على أجهزة التنفس الاصطناعي. وقد تلقى جميع المرضى عقاقير ايرثر مايسين، وأضيف عقار ريفامبين إلى علاج مريضين. ظل مريضان على قيد الحياة وتوفي مريضان. هذا هو التقرير الأول في المملكة العربية السعودية، الذي يصف أربع حالات من القصور التنفسي الشديد بجراثيم اللجيونيلا الرئوية.
المدونات الطبية السعودية ١٩٩٤م، ١٤ (٣): ٢٠٤_٢٠٨.

العوامل المؤثرة في استخدام المصادر الطبية والطرق التعليمية والموقف منها في مدرسة طبية سعودية

تستخدم كليات الطب وسائل تعليم مختلفة ومصادر تعليمية متعددة في عملية التعليم. من أجل تقصي موقف طلاب الطب من وسائل التعليم ومصادره والعوامل التي تلعب دوراً أساسياً في استخدامها في مدرسة طبية في بيئة عربية، تم إعداد استبيان للإجابة الذاتية وتوجيهه إلى ٢٨٣ طالباً طبياً في سنوات عملهم السريرية. احتوى الاستبيان أيضاً أسئلة تتعلق بالعوامل المحتملة التي تؤثر على المواظبة واستخدام مصادر التعليم. تبين أن وسائل التدريس التقليدية، والمحاضرات، والجولات السريرية تشكل العمود الفقري للعملية التعليمية في هذه الكلية. أما الانتظام في المحاضرات فكان يتعلق بنوعية المادة وكفاءة المحاضر، مما يؤكد أهمية المحاضرة الجيدة والمحاضر الكفء. حظي التعليم السريري بالقرب من المريض على إعجاب الطلاب على أنه وسيلة فاعلة لتعليم العلوم الطبية، والمهارات، ومدى تفاعل المرضى مع طلاب الطب. كانت مكتبة الكلية من أقل المصادر استخداماً من قبل الطلاب ولم تحظ باهتمامهم إلا بدرجة قليلة جداً. أشارت التوصيات العامة إلى تقليل الاعتماد على المحاضرات تدريجياً خلال سنوات العمل السريري وإدخال وسائل جديدة للتعليم السريري.
المدونات الطبية السعودية ١٩٩٤م، ١٤ (٣): ٢٠٩_٢١٤.

توافق تشخيصي بين اطباء الرعاية الأولية واخصائيي الأعصاب

تم تقييم قدرة أطباء الرعاية الصحية الأولية على تشخيص الاضطرابات العصبية من واقع السجلات الطبية لمئة وستة وستين مريضاً أحيلو إلى العيادة الخارجية للأمراض العصبية خلال سنة واحدة. كان التشخيص صحيحاً لدى ٧٤,٧٪ من المرضى عند الإحالة. أظهر أطباء الرعاية الأولية كفاية في تشخيص العوارض المخية الوعائية والصرع والآفات الكتلية والعته الشيخي

والآفات خارج الهرمية والاضطرابات المخيخية. كان التشخيص النوعي على مستوى الرعاية الأولية صعباً في حالات الصداع والحبل الشوكي واضطرابات الأعصاب المحيطية. ناقشنا في هذه المقالة مضامين هذه النتائج وأسبابها المحتملة. كما أوصينا بوضع حلول لتحسين هذا الوضع مع التركيز على التدريب السريري في الأمراض العصبية في مرحلتي الدراسة الجامعية والدراسات العليا. كما أكدنا على أهمية الدور التكاملي بين طبيب الرعاية الأولية وأخصائي الأعصاب.

المدونات الطبية السعودية ١٩٩٤م، ١٤(٣): ٢١٥_٢١٨.

الغياب الظاهر لتبدل الترتيب الجيني BCL-2 في اللمفوم الجريبي السعودي: تقرير أولي

يصاحب بعض الأنواع المميزة من الأورام لدى الإنسان إزفاءات صبغية نوعية. يعتبر الإزفاء بين الصبغيين ١٤ و١٨ لأمراض الأورام الجريبية علامة مميزة في الوراثيات الخلوية وخصوصاً لدى المرضى الأمريكيين على الأغلب. يحدث هذا الإزفاء الصبغي بين النهاية (3') في المنطقة غير الفعالة، التي لا تترجم إلى بروتين، (إما في منطقة الانكسار الرئيسة (mbr) أو في منطقة التجمع الثانوية (mcr) لجين bcl-2 المسبب للسرطان في الصبغي ١٨ وبين منطقة (JH) من جين الغلوبلين المناعي (Ig) في الصبغي ١٤. تم في هذه الدراسة استخدام تفاعل بوليمراز التسلسلي (pcr) لكشف أي تأشب يحدث بين جين bcl-2 وJHسواء في منطقة الانكسار الرئيسة أو في منطقة التجمع الثانوية في عشر حالات لمفوم جريبي لدى مرضى سعوديين. ومن الغريب أنه لم تظهر أي من تلك الحالات دليلاً على حدوث تبدل الترتيب الجيني لجين bcl-2 في أي من منطقة الانكسار الرئيسة أو منطقة التجمع الثانوية. إن غياب التأشف المعتاد بين bcl-2/JH لدى المرضى السعوديين المصابين بالأورام اللمفاوية الجريبية يعتبر أمراً مثيراً ومحيراً قد يوحي بأن حدوث تبدل الترتيب الجيني bcl-2 ونمطه لدى مرضى هذا اللمفوم يختلف حسب اختلاف جمهرة المرضى.

المدونات الطبية السعودية ١٩٩٤، ١٤ (٣): ٢١٩_٢٢٤.

دراسة سريرية وبائية لمرض القلب لدى أطفال المدارس في منطقة المنوفية في مصر

أجريت هذه الدراسة لتحديد نسبة انتشار داء القلب الرثوي وداء القلب الخلقي لدى أطفال المدارس الابتدائية في منطقة المنوفية في مصر، ودراسة العلاقة بين هاتين المشكلتين والأوضاع الاجتماعية والاقتصادية. تم فحص ما مجموعه ٨٠٠٠ طفل في مدارسهم لتقصي إصابتهم بداء في القلب، وتمت زيارة الأطفال الذين تم التثبت من إصابتهم بداء القلب الرثوي وداء القلب الخلقي بالإضافة إلى ٢٠٠ طفل معافى (مجموعة ضابطة) في منازلهم لتقييم المحيط الاجتماعي والعوامل الأخرى وذلك وفقاً لاستبيان معد. وجدنا أن نسبة الانتشار هي ٣,٤/١٠٠٠ و ٢,٦/١٠٠٠ لداء القلب الرثوي وداء القلب الخلقي على التوالي. كانت أكثر العيوب القلبية شيوعاً لدى الفئات المصابة بداء القلب الرثوي وداء القلب الخلقي هي على التوالي التضيق التاجي والرثوي المزدوج. شخص تسعة عشر (١٩) (٣٩,٦٪) مريضاً لأول مرة أثناء الدراسة. تلقى أربعة (١٤,٨٪) أطفال من المصابين بداء القلب الرثوي معالجة وقائية بالبنسيلين، ولم يتلق أي من الأطفال المصابين بداء القلب الخلقي هذه المعالجة. كان عدد الأشقاء المصابين، وتزايد عدد الولادات، والإجهاض المتكرر، وتناول الأدوية المانعة للحمل من قبل الأمهات، أعلى بدرجة ملحوظة لدى أسر الأطفال المصابين بداء القلب الخلقي. وكانت نسبة الأميين والمدخنين وغير المهرة من الآباء مرتفعة لدى الفئتين من المرضى. كان دخل الأسرة أقل لدى الفئة المصابة بداء القلب الرثوي، بينما كان منسب الازدحام والمحيط البيئي المتدني عموماً يرتبطان ارتباطاً وثيقاً بداء القلب الرثوي وداء القلب الخلقي. من الضروري وجود برامج خدمة صحية فعالة في المنوفية لحل مشكلة داء القلب لدى أطفال المدارس في المستقبل القريب.

المدونات الطبية السعودية ١٩٩٤، ١٤ (٣): ٢٢٥_٢٢٩.

انتشار أضداد المقوسة لدى المتبرعين بالدم في الأحساء

تنتج الإصابة بداء المقوسات عن طفيلي أولي إجباري داخل الخلايا هو المقوسة القندية. وتكون الإصابات الناجمة عن المقوسة، في غالبيتها، حميدة أو لا عرضية، ولكن قد يكون لها عواقب شديدة أو مميتة على مرضى نقص المناعة، والمرضى الذين تجرى لهم عمليات زراعة الاعضاء وكذلك على الجنين. وقد ينتقل هذا المرض عن طريق تناول لحم نيء، أو خضروات ملوثة أو نقل الدم بالإضافة إلى زراعة الاعضاء، كما قد ينتقل من خلال المشيمة من الأم إلى الجنين. وقد تظل أضداد المقوسة القندية في المصل بمستويات عالية لسنوات. قمنا بفحص ٧٨٤ متبرعاً بالدم من السعوديين باستخدام اختبار التراص الدموي غير المباشر، ووجد أن ٢٩٤ (٣٧,٥٪) متبرعاً كانوا إيجابيين للمصل بمستويات مختلفة. وجد أعلى معدل لإيجابية المصل لدى الفئة التي تتراوح أعمارها بين ٢١ و٣٠ سنة من الذكور، وانخفض وجود الأجسام المضادة بعد سن الأربعين. يجب التثبت من المعدل العالي لإيجابية المصل لدى الفئة التي تتراوح أعمارها بين ١٨ و٢٠ سنة من الإناث بإجراء المزيد من الدراسات.

المدونات الطبية السعودية ١٩٩٤، ١٤ (٣): ٢٣٠ـ٢٣٢.

استخدام الأمبيسيلين الموضعي للوقاية من التهاب الجرح في حالات التهاب الزائدة الحاد

تم بصورة عشوائية تصنيف ٢٤٩ مريضاً بالتهاب الزائدة الحاد، سيخضعون في المستقبل لعمليات استئصال الزائدة، إلى مجموعتين. تم إرواء الجرح في المجموعة الأولى التي تضم ١٣٢ مريضاً بمحلول ملحي نظامي معقم عند الإغلاق. وفي المقابل، تم إرواء الجرح في المجموعة الثانية التي تضم ١١٧ مريضاً بالأمبيسيلين المرضعي أثناء العملية. كانت المجموعتان متشابهتين من حيث العمر والجنس ومدة الاعراض وشدة التهاب الزائدة. وبالإضافة إلى ذلك تلقى المرضى جميعاً معالجة جهازية بعقاري جنتاميسين وفلاجيل قبل الجراحة. حدث التهاب الجراح لدى ٥,٣٪ من المجموعة الأولى مقارنة بـ٠,٩٪ فقط من المجموعة الثانية (درجة الاحتمال P أقل من ٠,٠٥). كان الانخفاض في معدل الالتهابات ملحوظاً (درجة الاحتمال P أقل من ٠,٠٥) في حالات التهاب الزائدة المثبت نسيجياً. نخلص إلى القول بأن إضافة الأمبيسيلين الموضعي أثناء الجراحة إلى الجنتاميسين والفلاجيل الجهازي يزيد من الوقاية ضد التهاب الجرح في حالات التهاب الزائدة الحاد.

المدونات الطبية السعودية ١٩٩٤، ١٤ (٣): ٢٣٣ـ٢٣٦.

المجلد ١٤ العدد ٣ ذوالقعدة ١٤١٤هـ مايو ١٩٩٤م

المدونات الطبية السعودية

رئيس التحرير : الدكتور محمد أختر

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الدكتور صلاح الفقيه
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مساعدتا التحرير :

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المدونات الطبية السعودية مجلة تنشر بموجب الأمر الملكي السامي رقم ٥/م/**٢٤٢٢٣** بتاريخ ١٤ شوال عام ١٤٠٠هـ. وتصدر مرة كل شهرين، وهي مشروع مشترك بين كل من كلية الطب ومستشفى الملك خالد الجامعي ـ جامعة الملك سعود، صندوق بريد **٢٩٢٥** ـ الرياض **١١٤٦١**، المملكة العربية السعودية، ومستشفى الملك فيصل التخصصي ومركز الأبحاث، صندوق بريد **٣٣٥٤** ـ الرياض **١١٢١١**، المملكة العربية السعودية. يتم صف وطبع المجلة بمطابع جامعة الملك سعود. يتم توزيع المدوَّنات بواسطة قسم البريد التابع لإدارة الخدمات الإدارية بمستشفى الملك فيصل التخصصي ومركز الأبحاث. كما يتولى قسم الترجمة في هذه الإدارة إعداد الملخصات العربية بالاشتراك مع الدكتور محمد زهير القاوي. كل المراسلات والاستفسارات وطرق الحصول على المستلات ترسل إلى مكتب المطبوعات على العنوان التالي :

مكتب المطبوعات
مدونات الطب السعودي
مستشفى الملك فيصل التخصصي ومركز الأبحاث
ص. ب (٣٣٥٤)
الرياض (١١٢١١) ـ المملكة العربية السعودية
ت : (٠١ـ٤٦٤ـ٧٢٧٢) تحويلة (١٨١٦/١٨١٥)
فاكس : (٩٦٦ـ٠١ـ٤٤٢ـ٧٢٣٧)

المسئول عن الإعلان :
مؤسسة فايد للإعلان ـ آي، بي، آي، إس.
الرياض ـ المملكة العربية السعودية
ت : (٠١ـ٤٧٧ـ٠٦٣٥/٣٧)
فاكس : (٠١ـ٤٧٨ـ٣١٦٧)
ممثل آي، بي، آي، إس في أوروبا وشمال أميركا :
مؤسسة سي، بي، إي.
المكتب الرئيسي في أوروبا ـ لندن
ت : (٤٤ـ٧١ـ٩٨٧ـ١٧٧٣) فاكس : (٤٤ـ٧١ـ٥٣٨ـ٨٣٦٢)
المكتب الرئيسي في شمال أميركا ـ ميامي
ت : (١ـ٣٠٥ـ٣٦١ـ٣١٩٩)
فاكس : (١ـ٣٠٥ـ٣٦١ـ٦٧٣١)

الآراء التي ترد في المقالات المنشورة تعبر عن رأي أصحابها فقط ولا تعبر عن وجهة نظر مجلة المدونات الطبية السعودية. لا يسمح بإعادة طبع أي جزء من المجلة أو نسخة بأي شكل وبأي وسيلة سواء أكانت إليكترونية أو آلية، بما في ذلك التصوير والتسجيل أو الإدخال في أي نظام حفظ أو استعادة معلومات إليكتروني، بدون الحصول على موافقة مسبقة من إدارة المجلة.

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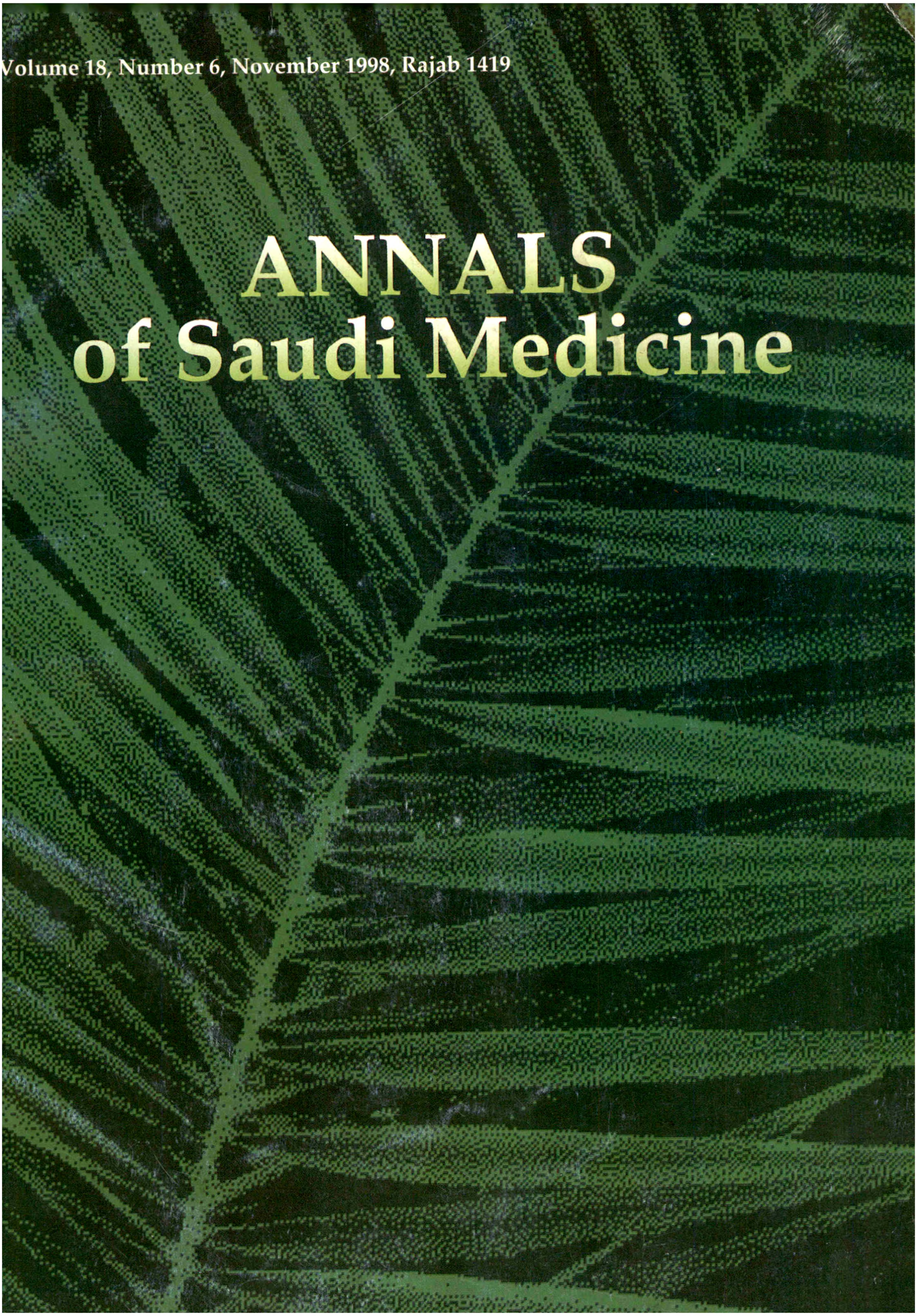

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The *Annals of Saudi Medicine* is a joint project of the King Faisal Specialist Hospital and Research Centre and the King Saud University College of Medicine and King Khalid University Hospital. The journal is printed at the King Saud University Press, Riyadh, Saudi Arabia. Since July 1985, the *Annals* has incorporated *The King Faisal Specialist Hospital Medical Journal,* established in 1980.

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The *Annals* publishes original articles, case reports, letters to the editor, editorials, and from time to time, special communications, commentaries, and review articles. The Editorial Board wishes to minimize delay between manuscript submission, decision, and publication, and accordingly authors are requested to follow carefully the instructions set out under "Information for Authors."

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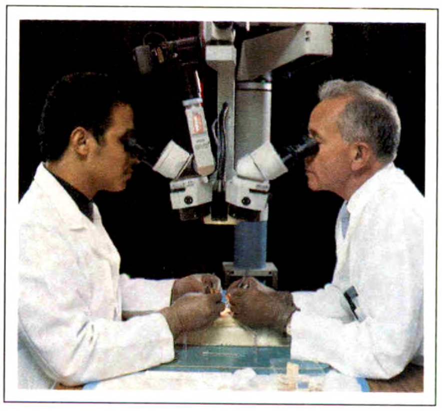

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Editorial

CHROMOSOME TELOMERES: THE AGING CLOCK

M. Anwar Iqbal, PhD, FACMG

A human life span is the length of time which a normal individual will live, without being afflicted with a major disease or accident. The life span of a given population may vary between 75 and 100 years and is determined, to a great extent, by genetic and environmental factors. The medical health system of a country also has a major impact on the life span of its population. The life span of humans has three phases: young (up to 25 years), middle (around 40 years), and old age (>60 years), the final phase of growth and development. Scientists have long been puzzled by this transition from youth to old age, a process generally called aging. One of the hallmarks of an aging cell is the presence of chromosomal abnormalities such as aneuploidy—a deviation from the normal 46 chromosomes present in a cell. Accumulation of lipofuscin in nerve, kidney, liver and muscle cells, resulting in cell dysfunction, is yet another important aspect of aging.

In the early 1960s, Hayflick[1] demonstrated by *in vitro* culture methods differences in the replication doublings between embryonic fibroblast and fibroblast cultures established from mature individuals. The embryonic cells were shown to divide approximately 50 times in culture, whereas the mature cells exhibited significantly reduced numbers of cell division. The morphological features of cells approaching the end of their span were shown to be characteristic of "aging cells."[2] These interesting results led to the theory of a biological clock in every cell which determines its life span.

Telomeres were implicated in the aging process for the first time by Watson in 1972.[3] The tips of the human chromosome arms (Figure 1), known as telomeres, consist of DNA repeats TTAGGG synthesized by an RNA-dependent DNA polymerase enzyme known as telomerase. The presence or absence of active transcription of telomerase correlates with the size of TTAGGG. Telomerase is active in germ cells, with a size of about 15 kilobase (kb), whereas in most somatic tissues telomerase is not transcribed and the telomere length is significantly decreased.

Watson showed indirectly that a portion of telomere is masked from the action of DNA polymerase, thereby defying the tips from replication with each successive cell division. In other words, the length of the telomeres decreases with each replication cycle. Telomere shortening in the aging process remained a hypothesis until 1990, when it was strengthened by additional evidence.[4-7]

Experimental proof directly implicating telomeres in the aging mechanism came from the works of Bodner et al.[8] and Vaziri and Benchimol.[9] Bodner et al. showed that by transfecting normal human somatic cells with a subunit of telomerase enzyme (which is absent in normal somatic cells), the length of the telomeres were increased. As a result, the replicative life span of these cells were dramatically extended beyond their usual limit of 50 population doublings. Similarly, Vaziri and Benchimol independently confirmed the role of telomeres in replicative senescence of cells. Both of these studies showed that telomeres become shortened as the cells age. Furthermore, it was also shown that relengthening the telomeres reverses the aging process, activates gene expression, and changes the morphology of cells to young-looking cells. These unique features of telomeres undoubtedly establishes them as the biological clock of aging.

The possibilities for clinical exploitation of telomeres and telomerase-dependent aging phenomenon is enormous. For example, certain genetic conditions characterized by premature aging, such as Werner syndrome, can be treated by restoring the cells' telomere length to normal levels either *in vivo* or *in vitro*, followed by transplantation. Similarly, the life span of aging tissues or cells, which gives rise to conditions such as artherosclerosis, dementia and immunosuppression, can be reset by telomere extension so that these cells can become normal and cure the disease. These innovative therapies will be the focus in the next millennium.

The role of telomeres in malignancies has also been investigated. Malignant cells which escape their life span have been shown to have longer telomeres, with increased telomerase activity, than their normal counterparts.[10-11] Theoretically, it should be possible to end the life span of a cancer cell by inhibiting its telomerase activity and shortening its telomeres. More importantly, the impact of such an approach will be greater in genetic conditions with a high risk of malignancy, such as Fanconi anemia. But the relationship between high telomerase activity and malignancy raises an important question. By resetting the aging clock in non-malignant cells, is there a risk of

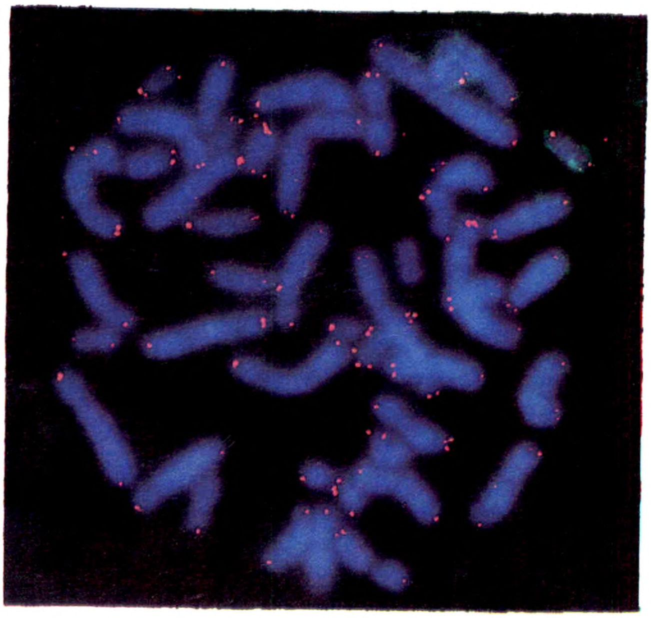

FIGURE 1. Human metaphase chromosomes hybridized with digoxigenin-labeled All Human Telomeres Probe (Cat #P5097-DG.5, Oncor Inc., Gaithersburg, MD, USA). The tips of the chromosomes or telomeres appear as bright red. The chromosomes are counterstained with DAPI. Methodology used was as recommended by the manufacturer (Edition 6.95, Oncor Inc.).

initiating malignancy? So far, the evidence about telomerase enzyme has been encouraging. By increasing telomerase expression in a non-malignant aging cell to reset its life span, no deleterious effect have been observed, in fact, these cells appeared and replicated as normal cells.[8]

The understanding of the aging phenomenon has come a long way and has started to unfold. Telomere research opens up an important area in this field. There may be many more mechanisms by which aging can occur, however, telomere and telomerase research currently occupy the central position. It remains to be seen whether telomere research will eventually increase the human life span from its current level, or if it may totally eliminate the final phase of life—old age.

M. Anwar Iqbal, PhD, FACMG
Head, Section of Cytogenetics/Molecular Genetics
Department of Pathology and Laboratory Medicine, MBC-10
King Faisal Specialist Hospital and Research Centre
P.O. Box 3354
Riyadh 11211, Saudi Arabia

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AIRBORNE *ALTERNARIA* SPORES: POTENTIAL ALLERGIC SENSITIZERS IN SAUDI ARABIA

Syed M. Hasnain, PhD, FACAAI; Abdulrahman Al-Frayh, MD;
Muhammed O. Gad-el-Rab, MD; Sultan Al-Sedairy, PhD

Background: In order to investigate the role of airborne *Alternaria* spp. in the sensitization of individuals having respiratory allergy symptoms, particularly bronchial asthma, an aerobiologic and clinical (diagnostic) study was conducted at several centers in Saudi Arabia.

Materials and Methods: Airborne *Alternaria* spores were studied at four different centers in Riyadh, Jeddah and Al-Khobar, including three years at one site. Skin prick tests (SPT) were conducted on a total of 616 allergic individuals attending allergy clinics at six different hospitals in Abha, Qassim, Gizan, Jeddah, Hofuf and Makkah regions.

Results: *Alternaria* spores constituted between 1.9%-9.6% of the total fungal air spora, and the maximum concentration exceeded $5x10^2$ spores per m^3 of air in Jeddah, followed by $4.9x10^2$ spores per m^3 in Al-Khobar. Mean weekly and monthly concentration of *Alternaria* fluctuated, reaching up to 150 spores per m^3 and 60 spores per m^3, respectively. Quantitative regional variations were also recorded. IgE-mediated SPT reactivities conducted on allergic patients resulted in an overall 21.6% positive reactions, showing mild, moderate and strong wheal and erythema.

Conclusion: The findings reveal that *Alternaria* spores are prevalent as a major component in the outdoor environment of the Kingdom, with peaks in April and October. The overall 21.6% positive SPT reactions indicate the sensitization level or cross-reactive sensitivity to *Alternaria* allergens. The study suggests that airborne *Alternaria* can be a potential allergic sensitizer in susceptible individuals and can be a risk factor in sensitized individuals with symptoms of bronchial asthma and allergic rhinitis in the Kingdom of Saudi Arabia.

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Key Words: *Alternaria* spores, skin prick tests, asthma, allergies.

Alternaria alternata allergens have long been considered to cause significant respiratory allergies in patients in the United States.[1] *A. alternata* spores were also implicated recently in serious cases of respiratory arrest[2] in children and young adults, and were temporarily associated with observed high levels of *Alternaria* spores in outdoor air.[2] Airborne incidence of *Alternaria* spores has been documented from various countries,[3] and the antigenic properties of spores have been partially characterized.[4-7] They have also been documented from the environment of Middle East countries,[8] but mainly without volumetric data,[9,10] and without their diagnostic implications.[11,12] Sorensen et al.[12] reported about 7.7% *Alternaria* colonies, while data from Dammam[13] with volumetric sampling identified *Alternaria* spores between 1.9%-4%. In 1989, Hasnain et al.[14] identified *Alternaria* as a major component

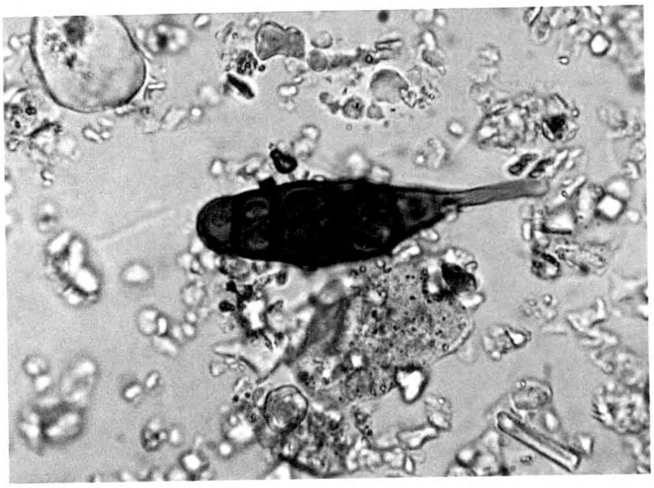

FIGURE 1. A photomicrograph of a conidium of *Alternaria* trapped from the air using volumetric sampler.

From the Department of Biological and Medical Research (Drs. Hasnain and Al-Sedairy), King Faisal Specialist Hospital and Research Centre, and the College of Medicine (Drs. Al-Frayh and Gad-el-Rab), King Saud University, Riyadh, Saudi Arabia.

Address reprint requests and correspondence to Dr. Hasnain: Department of Biological and Medical Research, MBC 03, King Faisal Specialist Hospital and Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia.

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TABLE 1. *Catch percentage of airborne* Alternaria *spp. at various sites in Saudi Arabia.*

Month	KFSH 1986-87	JEDDAH 1987-88	AKHB 1987-88	KKUH 1987-88	KKUH 1988-89	KKUH 1989-90
Jan	6.4%	1.8%	3.3%	5.0%	0.7%	3.8%
Feb	6.6%	2.3%	2.7%	6.6%	2.7%	0.8%
Mar	7.8%	1.2%	5.3%	3.7%	3.9%	1.8%
Apr	9.6%	1.0%	4.4%	6.5%	6.4%	4.4%
May	7.4%	0.8%	2.8%	6.7%	3.5%	2.2%
June	3.8%	1.8%	7.0%	4.0%	2.6%	3.0%
July	1.9%	1.5%	2.6%	4.4%	2.1%	2.1%
Aug	5.1%	2.8%	4.5%	3.7%	2.4%	1.5%
Sept	2.2%	1.7%	6.6%	1.5%	3.9%	2.4%
Oct	5.2%	2.3%	2.6%	1.9%	2.7&	4.0%
Nov	4.4%	1.0%	1.9%	1.6%	5.1%	3.9%
Dec	6.0%	2.4%	4.1%	2.5%	1.9%	2.6%
Mean	5.5%	1.7%	4.0%	4.0%	3.2%	2.7%
Range	1.9%-9.6%	1.0%-2.8%	1.9%-6.6%	1.5%-6.7%	0.7%-6.4%	0.8%-4.0%

TABLE 2. *A summary of SPT-positive reactions in six different regions using* Alternaria *antigen.*

Reaction	Age (yr)	Female/male	Total individuals	Total positive
Mild	1-12	9.6%/11.7%	67	
	13-18	3.2%/2.7%	18	
	>18	5.2%/3.5%	26	
	Blank	0.8%/1.4%	7	
	Total	18.9%/19.4%	118	19.16%
	Total F/M		47/71	
Moderate	1-12	0.8%/0.3%	3	
	13-18	–	–	
	>18	0/1.9%	7	
	Blank	0.4%/0	1	
	Total	1.2%/2.2%	11	1.79%
	Total F/M		3/8	
Strong	1-12	0/0.3%	1	
	13-18	–	–	
	>18	0.8%/0.3%	3	
	Blank	–	-	
	Total	0.8%/0.5%	4	0.65%
	Total F/M		2/2	
No reaction	Total	79.1%/77.9%	483	78.40%
	Total F/M		197/286	
Total			616	100%
Total F/M			249/367	

F/M=female/male.

in the Riyadh outdoor environment, ranging from 1.9%-9% of the total airborne spores isolated.

The relationship of airborne *Alternaria* and allergic diseases, particularly bronchial asthma, has been established by many workers in this field.[15-18] However, this has generally been done *in vivo*, by conducting skin prick test (SPT), and seldom by bronchial challenges or inhalation provocation tests. An *in vitro* test, such as the radioallergosorbent test (RAST), is often incorporated with the *in vivo* test.

The objective of this study was to investigate and accumulate comprehensive aerobiologic and clinical information on *Alternaria*, using continuous and volumetric sampling and diagnostic SPT for IgE-mediated reactivities, in order to examine their role as a potent allergen and a potential sensitizer in patients with asthma and other allergic diseases in Saudi Arabia.

Materials and Methods

Spore Detection

Burkard Volumetric Spore Traps were operated at four different sites in three cities in Saudi Arabia (Riyadh, Jeddah and Al Khobar). Riyadh is the capital city, situated in the middle of the desert, in the Central Province. Jeddah is a coastal city by the Red Sea, and Al-Khobar is another comparatively new coastal city, in the Eastern Province of Saudi Arabia.

Sampling was conducted from 1986 through 1990. Air spora were trapped on melinex tapes, mounted and prepared for microscopic study. Slides were studied at 400x. One field of view at 400x was calculated to be 0.152053 mm^2. Ten such fields were each examined for an hour for the whole period. The numbers of *Alternaria* conidia were converted to concentrations per m^3 of air.[14]

Site Selection

The following sites were selected for sampling of air in order to evaluate airborne incidence of *Alternaria* in Saudi Arabia: King Faisal Specialist Hospital and Research Centre (KFSH&RC) compound, Riyadh; King Khalid University Hospital (KKUH) compound, Riyadh; King Abdulaziz University compound, Jeddah (JEDD); King Faisal University Hospital compound, Al-Khobar (AKHB).

Allergic Patients

A total of 616 patients, comprising 249 females and 367 males from six different hospitals in Saudi Arabia, were included in this study. These included Asir Central Hospital in Abha, King Fahad Hospital in Qassim, Chest Diseases Hospital in Gizan, King Faisal University Hospital in Hofuf, King Abdulaziz University Hospital in Jeddah, and Noor Hospital, Makkah. All patients were attending allergy clinics in these areas and were suffering from various allergic diseases, including bronchial asthma. After obtaining their informed consent, those on antihistamines were instructed to stop the medication four days prior to the test. Routine SPT was conducted on the above patients, using *Alternaria* extract (ALK w/v 1:20).

The SPT results were examined and recorded as follows: weal size 0 = negative (saline control); weal size >2 mm = mild positive; weal size >3-5 mm = moderate positive; >5 mm = strong positive; 1% histamine phosphate was included as positive control.

Results

Percentages of airborne *Alternaria* spores (Figure 1) at four different sites, including three consecutive years at one site (KKUH), are presented in Table 1. Mean weekly airborne concentrations per m^3 of *Alternaria* spp. for KFSH&RC, JEDD and AKHB are presented in Figure 2. Mean weekly airborne concentration per m^3 for 3 consecutive years (1987-90) at KKUH sites are presented in Figure 3. Mean monthly concentration of airborne *Alternaria* for the four sites are presented in Figure 4 (since KKUH was covered for 3 years, the findings are being presented as six different sites for the reason of comparison). Maximum hourly concentrations per m^5 of *Alternaria* spores for all sites are presented in Figure 5.

The data presented in the above tables and figures show that *Alternaria* constituted up to 5.5% (yearly mean) of airborne fungal spores, with the highest concentration in April (9.6%) at the KFSH&RC site. The weekly mean concentration exceeded 140 per m^3 of air, and the maximum concentration exceeded 500 per m^3 at the Jeddah site. The AKHB site was close to 500 per m^3 of air, while the KFSH&RC site exceeded 350 per m^3 of air.

Results of SPT on 616 patients from several regions using *Alternaria* commercial antigen are presented in Table 2 (a summary of all tests), while the regional results are presented in Table 3.

Discussion

Approximately 20% of the human population is considered to be suffering from atopy, involving localized reactions to extrinsic allergens, such as pollens, animal fragments, fungal spores, house dust mites, etc. Contact between allergens and the cell-bound IgE in the bronchial tree, nasal mucosa and conjunctival tissues releases mediators of anaphylaxis to produce asthma and hay fever. Sensitivity is normally assessed by response to prick and intradermal challenges with antigen. The release of histamine and other mediators produces a wheal and erythema, which indicate the severity of the reaction as mild, moderate or strong. However, optimal use of laboratory allergy tests requires a high level of knowledge regarding allergens' composition, distribution, local importance and other properties which facilitate selection of adequate tests.[1]

The current data on airborne *Alternaria* spores clearly demonstrate that they are widely distributed in the Saudi Arabian environment with quantitative regional variations. Maximum hourly concentration exceeds 500 spores per m^3 (Figures 5). The value can be related to the suggested threshold concentration of 50 *Alternaria* spores per m^3 (mean daily) for sensitization, and once sensitized, a lesser concentration can elicit the symptom or symptoms.

Fungal antigen preparation from commercial sources varies widely. The possible causes of variability are the following: 1) intrinsic variation between spores and mycelium in antigen content; 2) somatic mutations causing allergen content changes within single culture; 3) aging and culture variable changes; 4) interstrain variability; and 5) interspecies variability.[15] The sorting effect is the weak antigen causing a greater number of mild reactions than severe or strong reactions.

TABLE 3. *SPT-positive reactions in allergic patients from different regions in Saudi Arabia using commercial* Alternaria *antigen.*

Reaction	Female	Male	Grand total
Qassim			
Mild	4 (8%)	11 (12.5%)	15 (10.9%)
Moderate	0	3 (3.4)%	3 (2.2%)
Strong	0	0	0
No reaction	46 (92%)	74 (84.1%)	120 (86.9%)
Total	50 (100%)	88 (100%)	138 (100%)
Abha			
Mild	7 (10%)	14 (13.7%)	21 (12.2%)
Moderate	1 (1.4%)	4 (3.9%)	5 (2.9%)
Strong	2 (2.9%)	1 (1%)	3 (1.7%)
No reaction	60 (85.7%)	83 (81.4%)	143 (83.2%)
Total	70 (100%)	102 (100%)	172 (100%)
Gizan			
Mild	3 (100%)	3 (37.5%)	6 (54.5%)
Moderate	0	0	0
Strong	0	0	0
No reaction	0	5 (62.5%)	5 (45.5%)
Total	3 (100%)	8 (100%)	11 (100%)
Hofuf			
Mild	3 (6.8%)	7 (12.7%)	10 (10.1%)
Moderate	0	0	0
Strong	0	0	0
No reaction	41 (93.2%)	48 (87.3%)	89 (89.9%)
Total	44 (100%)	55 (100%)	99 (100%)
Jeddah			
Mild	1 (4.8%)	4 (11.8%)	5 (9.1%)
Moderate	1 (4.8%)	0	1 (1.8%)
Strong	0	0	0
No reaction	19 (90.4%)	30 (88.2%)	49 (89.1%)
Total	21 (100%)	34 (100%)	55 (100%)
Makkah			
Mild	29 (47.6%)	32 (40%)	61 (43.3%)
Moderate	1 (1.6%)	1 (1.3%)	2 (1.4%)
Strong	0	1 (1.3%)	1 (0.7%)
No reaction	31 (50.8%)	46 (57.5%)	77 (54.6)
Total	61 (100%)	80 (100%)	141 (100%)

Alternaria alternata (also known as *A. tenuis*) is an extremely common species occurring in plants, soil, food, house dust and atmospheric samples, with optimal growth at 25°C–26°C.[2] It is also a complex species that exhibits significant interstrain differences in morphology, enzyme profile and allergen content when grown under various environmental conditions.[20] The complexity of the *A. alternata* allergen was studied by analyzing proteins, carbohydrates and allergenic activity of 10 different strains, by using RAST inhibition and crossed immunoelectrophoresis (CIE)/crossed radioimmunoelectrophoresis (CRIE). A total of 32 allergens were identified, including one major antigen (Ag-8), seven intermediate and six minor allergens.[1] Vijay also studied *A. alternata* and *A. solani* and reported that various strains of each species showed similarities but also showed considerable differences.[21]

As *in vivo* diagnostic tests, e.g., SPT, are usually considered to be more sensitive and economical than *in*

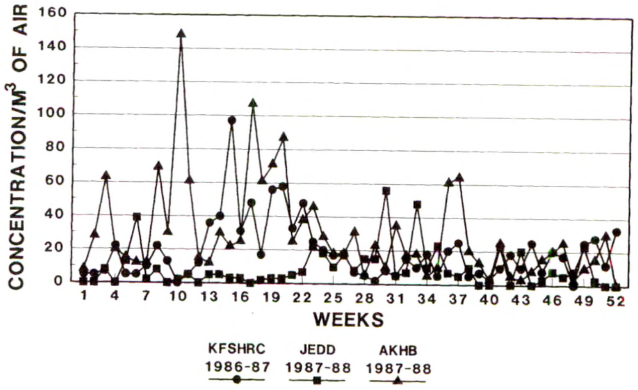

FIGURE 2. Weekly mean concentrations per m^3 of *Alternaria* spp. at three different sites.

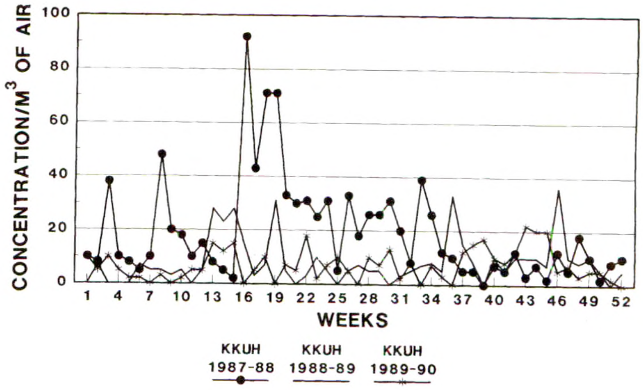

FIGURE 3. Weekly mean concentrations per m^3 of *Alternaria* spp. at KKUH site for three continuous years.

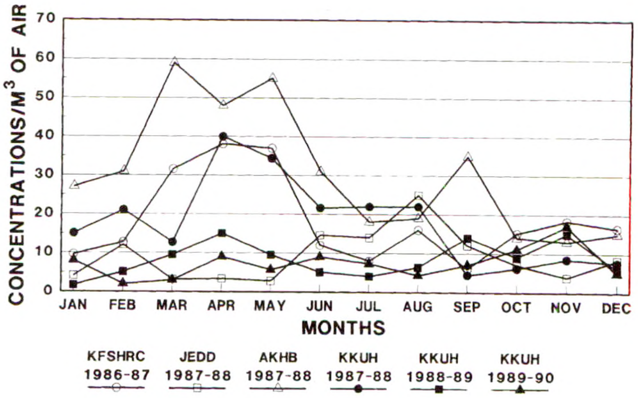

FIGURE 4. Monthly mean concentrations per m^3 of *Alternaria* spores at 6 different sites.

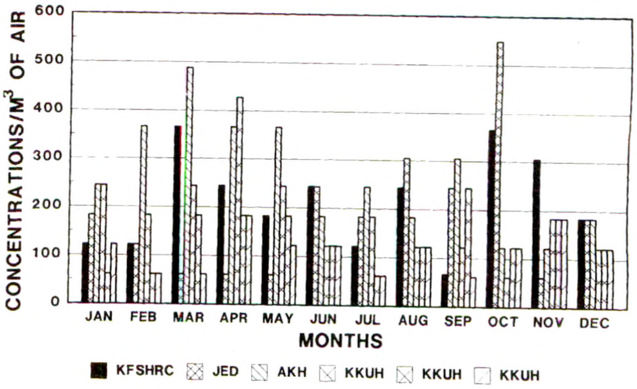

FIGURE 5. Maximum hourly concentrations per m^3 of *Alternaria* spp. at several locations in Saudi Arabia.

vitro (RAST) tests, there appears to be a great variation in the relative frequency of positive skin reactivity to fungal extracts in patients with asthma and rhinitis in different countries. Positive results range from 3%-4% in Sweden to above 80% in some states in the USA.[15]

Skin prick testing with extracts of fungal species derived from homes of allergy clinic cases in Toronto, Canada, displayed up to 50% positive reactivity to *Alternaria alternata,* in comparison to only 4% indoor incidence in patients' homes. This indicates the possible exposure and subsequent sensitization to high fungal concentrations in outdoor environment, or in work-related environments.[17] In a similar study of 2942 allergic cases with mainly bronchial asthma and rhinitis using partially purified *Alternaria* allergen extract, positive reactions varied from 5% to 20%, depending on the geographical and climatic characteristics.[22] In Turkey, 130 children with respiratory allergies were submitted to scratch skin test and intradermal skin test. On scratch test, 18.6% of cases reacted to *Alternaria* antigen, while 31.5% of cases reacted to it in intradermal skin test.[18]

The SPT data presented in this paper support the above findings that IgE-mediated reactivity to *Alternaria* is very common, and is the most reactive among all fungal reactions. It may also occur as a result of cross-reactivities with other *Alternaria* species or related genera, such as *Ulocladium,* which is also very common in Saudi Arabia.[19,23] Hence, it is not inconceivable that there may be shared antigenic properties between the two genera, as with *Stemphylium.*[5] However, the spores of *Stemphylium* are not so common in our environment.[14] On the other hand, it is known that there are more species-specific antigens in fungi than the genus-specific antigen. These complexities and variations remain as yet unanswered, because only one species (*alternata*) of *Alternaria*, out of more than 45 species known to exist worldwide, has been studied in detail.[24,25]

This study documents the presence of *Alternaria* spores at various centers of the country exceeding threshold concentrations for sensitization and acute attack of bronchial asthma in sensitized patients. Though no attempts were made to study and correlate the aerobiologic and diagnostic aspects at each center simultaneously at this stage, the SPT data obtained confirm that *Alternaria* spores are potential sensitizers in susceptible individuals showing allergic symptoms, particularly bronchial asthma and allergic rhinitis. Therefore, those patients who are SPT-positive with *Alternaria* extract may be at risk for elicitation and/or exacerbation of their symptoms.

The mild IgE-mediated reaction (19.16%) (Table 2) is attributable to the poor quality of fungal extract, as these are prepared, unlike pollen extract, from culture and not from pure spores. Batch to batch variation in the potency of fungal extracts was recorded.[1] Hence, the possibility of both "false-positive" and "false-negative" reactions because of antigenic and diagnostic variabilities cannot be eliminated.

We, therefore, conclude that standardized or the highest available quality of *Alternaria* extract should be included in all diagnostic test profiles in Saudi Arabia in order to identify *Alternaria* sensitivity, and to obtain possible stronger reaction in sensitized patients. We recommend that, if possible, even the routine diagnostic test should extend beyond SPT to include intradermal test or RAST for better diagnostic accuracy.

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DYSPEPSIA AND *HELICOBACTER PYLORI* INFECTION: ANALYSIS OF 200 KUWAITI PATIENTS REFERRED FOR ENDOSCOPY

Eman A. Abahussain, MSc; Fuad A.M. Hasan, MB, ChB, FACP;
Paul J. Nicholls, PhD, FRSC, FIBiol

Background: Dyspepsia is a very common symptom, and is the reason for most referrals for esophagogastroduodenoscopy (EGD). Peptic ulcer disease (PUD), gastroesophageal reflux and gastric cancer account for a minority of such patients. However, the majority have no significant endoscopic abnormalities (non-ulcer dyspepsia). Recently, infection with *Helicobacter pylori* (HP) has been implicated in the pathogenesis of PUD and gastric cancer. Since HP can be diagnosed by noninvasive techniques, it has been suggested that endoscopy should be restricted to HP-positive patients who do not respond to empirical therapy with antimicrobials. The aim of this study was to establish the prevalence of HP among Kuwaiti dyspeptic patients referred for endoscopy and to determine whether demographic and clinical screening, or the presence of HP, can help distinguish groups of patients with significant gastroduodenal pathology from those with non-ulcer dyspepsia.

Patients and Methods: Two hundred randomly selected Kuwaiti patients referred for endoscopy were evaluated prospectively. A detailed personal interview was conducted to establish the demographic and clinical profile of each patient and a diagnostic EGD was performed after the interview. Finally, antral mucosal biopsies were taken to determine the presence of HP. The pre-coded data were analyzed.

Results: The main endoscopic findings were normal (32%), non-erosive antral gastritis (26%), duodenitis (17.5%), duodenal ulcer (11.5%), deformed bulb (4%), esophagitis (7%), and erosive gastritis (2%). The demographic and clinical characteristics of patients did not correlate with endoscopic findings. The overall prevalence of HP infection was 88.5%. There were no statistically significant differences in the prevalence of HP among patients with various endoscopic findings.

Conclusion: HP infection is common in Kuwaiti dyspeptic patients referred for endoscopy, irrespective of their demographic and clinical features or the underlying cause of dyspepsia. Noninvasive methods to detect HP are not valid alternatives to endoscopy in the work-up of dyspeptic patients.

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Key Words: *Helicobacter pylori*, endoscopy, gastritis.

Dyspepsia is defined as pain or discomfort centered in the upper abdomen. It may be associated with distention, belching, nausea or anorexia. It is estimated that 20%-40% of the population complain of dyspepsia.[1-3] Most dyspeptic patients either have no identifiable cause of dyspepsia (non-ulcer dyspepsia, NUD),[4] or have peptic ulcer disease (PUD),[5] namely, gastric or more commonly, duodenal ulcers. Less common causes of dyspepsia include gastric cancer and pancreatic disease. Upper gastrointestinal endoscopy is currently the main diagnostic modality in the work-up of dyspeptic patients. Given the high prevalence of dyspepsia in the population and the expenses incurred by endoscopy, dyspepsia is a major burden on health system resources. Lately, *Helicobacter pylori* (HP) has been linked to duodenal and gastric ulcers, and to a lesser extent, gastric malignancy. Screening for HP can now be done by noninvasive techniques, such as serologic tests or urea-breath tests. Eradication of HP has been shown to cure PUD. However, in most studies, it had little impact on NUD. It has been suggested that instead of subjecting dyspeptic patients to endoscopy as an initial diagnostic test, one may screen these patients for HP by noninvasive tests and treat those who test positive. Endoscopy would then be restricted to patients who test negative for HP, those who do not improve after a therapeutic trial for HP, and to patients whose clinical picture is suggestive of malignancy, e.g., weight loss. The potential cost effectiveness of this approach was based on the epidemiologic profile of HP in Western countries, where the prevalence of this infection is relatively low compared with that seen in third world

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From the Departments of Medicine (Dr. Hasan), Community Medicine and Behavioural Sciences (Ms. Abahussain), the Faculty of Medicine, University of Kuwait, Kuwait, and from the Welsh School of Pharmacy (Dr. Nicholls), University of Cardiff, Cardiff, U.K.

Address reprint requests and correspondence to Ms. Abahussain: Welsh School of Pharmacy, University of Cardiff, Redwood Bldg., King Edward VII Avenue, Cathays Park, Cardiff CF1 3XF, U.K.

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TABLE 1. *Prevalence of HP according to the sociodemographic characteristics of the study population (n=200).*

Variables	%	% HP-positive
Age (yr)		
<15	2.5	40
16-25	19	78.9
26-35	32.5	92.3
36-45	25.5	92.2
>46	20.5	92.7
Sex		
Male	47.5	89.5
Female	52.5	87.6
Education level		
Illiterate	14.5	89.7
Intermediate school	17.5	88.6
Secondary school	27	83.3
College and postgraduate qualification	41	91.5
Occupation		
Dependent	17.6	71.9
Housewife	25.8	89.4
Unskilled laborer	2.2	100
Server	7.7	92.9
Skilled workers	7.7	92.9
Office workers	16.5	93.3
Professionals	22.5	87.8
Monthly income		
<500 KD*	13.5	81.5
500-1000 KD	41.5	91.6
>1000 KD	45	87.8
Residence**		
Hawali	25.3	80
Farwania	33.8	89.6
Jahra	4.5	88.9
Capital	28.8	91.2
Ahmadi	7.6	100
Family members		
<5	34.5	87
6-10	47.5	87.4
11-15	14	92.9
>16	4	100

*1 KD=3.3 US dollars; **all are urban areas.

TABLE 2. *Endoscopic findings and the prevalence of HP by the endoscopic diagnosis.*

Endoscopic diagnosis	Number of patients	Positive histology
Duodenal ulcer	23 (11.5%)	22 (95.7%)
Duodenitis	35 (17.5%)	29 (83%)
Duodenal deformity	8 (4%)	6 (75%)
Esophagitis	14 (7%)	14 (100%)
Gastric erosion	4 (2%)	4 (100%)
Gastritis	52 (26%)	44 (84.6%)
Normal	64 (32%)	58 (90.6%)
Total	200 (100%)	177 (88.5%)

countries. Data on the prevalence and clinical significance of HP in developing countries are limited, particularly from the Arabian Gulf region.[6-14] We conducted this study to determine the prevalence of HP among dyspeptic patients referred for endoscopy at our center, which provides open access endoscopy services to the nationals of Kuwait (population 1.8 million). We also set out to determine whether sociodemographic and clinical characteristics can distinguish patients with significant gastroduodenal pathology from those with non-ulcer dyspepsia. Finally, we aimed to find out whether infection with HP can distinguish patients with PUD from those with NUD.

Patients and Methods

Between October 1995 and May 1996, 200 randomly selected Kuwaiti patients with dyspepsia were studied prospectively. These patients had been referred to Thunayan Al Ghanim Gastroenterology Center to undergo esophagogastroduodenoscopy (EGD). Pregnant women, individuals over 70 years of age with other complications, and patients with complex medical or surgical conditions were excluded. Patients were subjected to a structured questionnaire before they underwent endoscopy. This questionnaire was tested in a pilot study on 50 dyspeptic individuals prior to its use in the study in order to confirm its validity.

Personal interviews were conducted individually with the 200 patients. The questionnaire consisted of 29 questions, mainly in the closed question format. The questions pertained to the sociodemographic profile of each patient (age, sex, level of education, residence, occupation, family income, size of family and smoking behavior), as well as severity of symptoms and the intake of antibiotics within the previous three months. The pre-coded data were analyzed by computer using the Statistical Package for Social Sciences.

Endoscopy was performed by standard procedures after an overnight fast, using Olympus and Pentax Video endoscopes, which were sterilized with glutaraldehyde for 10 minutes. At least one mucosal biopsy was taken from the antrum within 20 mm of the pylorus. The specimen was placed in 10% formalin and sent for standard histopathologic examination by a single pathologist who was not aware that the patients were enrolled in the study. The biopsy forceps were sterilized in glutaraldehyde between patients.

The prevalence of HP was determined as percentages of positives out of the exposed. The chi-squared test was used to test the difference in the prevalence of HP between NUD and PUD, and also the variation in the prevalence of HP by different factors (sociodemographic and symptoms). The *P*-values calculated were two-tailed, and $P \leq 0.05$ was considered significant.

Results

The sociodemographic characteristics of the study population are summarized in Table 1. Of the 200 patients, 95 (47.5%) were male and 105 (52.5%) were female, with a mean age of 36.5 and 34.4 years, respectively (range 6-70 years). The overall prevalence of HP was 88.5%. Age significantly related to the frequency of HP ($P<0.001$). There was no statistically significant association between

TABLE 3. *Severity of symptoms and its relation to the presence of HP (total number of patients is 200).*

	Severe*		Moderate**		No symptoms		P-value
Symptoms	#†	% HP‡	#	% HP	#	% HP	
Upper abdominal pain	161	89.4	29	79.3	10	100	NS++
Distention+	134	93.3	42	71.4	23	95.7	<0.001
Nausea	64	87.5	57	87.7	79	89.9	NS
Vomiting	33	87.9	29	89.7	138	88.4	NS
Irregular bowel+ movement	10	100	92	88	97	88.7	NS
Heartburn+	90	94.4	60	80	49	89.8	<0.05
Belching	60	93.3	71	87.3	69	85.5	NS

*Severe symptoms which influence concentration on daily activities and/or requires rest;[25] **moderate symptoms are defined as symptoms which cannot be ignored, but do not influence daily activities; †number of patients having the symptoms; ‡prevalence of HP among patients with the specific symptoms; +for these symptoms, one patient was unable to answer the question on severity; ++NS=not significant at the 0.05 level.

TABLE 4. *Correlation of endoscopic findings with the "hard-core" symptoms as reported by the patients.*

Endoscopic diagnosis	# of patients	% awoken by symptoms	% reporting weight loss
Duodenal ulcer	23	74	56.5
Duodenitis	35	54.3	43
Duodenal deformity	8	87.5	37.5
Esophagitis	14	64.3	43
Gastric erosion	4	100	25
Gastritis	52	62.7	29.4
Normal	64	64.1	47

HP and various other demographic or socioeconomic factors, such as gender, education level, residence, occupation, family size or income, or smoking behavior.

Endoscopic diagnoses are shown in Table 2. There were no statistically significant differences in the prevalence of HP between patients with different endoscopic diagnosis. Also, the prevalence of HP in patients with NUD did not differ significantly from patients with PUD. The severity of various symptoms did not show a significant association with either the presence or absence of HP, except the severity of distention, and heartburn ($P<0.001$ and <0.05, respectively) (Table 3). In addition, being awoken by dyspeptic symptoms (abdominal discomfort) and weight loss did not correlate with the endoscopic findings (Table 4).

Discussion

HP is the most common bacterial infection in man. Most epidemiological studies carried out in Western countries have revealed that the prevalence of HP in children is low and increases with age at approximately 1%-2% per year.[15,16] The frequency of HP is also thought to be inversely related to socioeconomic status. HP has been linked to two important causes of dyspepsia, namely, PUD and gastric cancer. Most authorities agree that eradicating HP would cure PUD. Anti-HP drugs are now routinely used in the treatment of most patients with PUD. The benefit of eradicating HP in NUD is uncertain.

HP can now be diagnosed using simple, cheap and noninvasive techniques, such as C13 or C14 urea breath test, or serologic assay for anti-HP antibodies. Thus, it has been suggested that it would be more cost effective to screen dyspeptic patients for HP by these noninvasive tests prior to referral for endoscopy. Patients who test positive for HP would then be treated with antimicrobial agents to eradicate HP. Patients would be referred for endoscopy if they tested negative for HP on initial evaluation, or continued to have symptoms despite receiving anti-HP therapy.

In the present study, most patients (88.5%) were infected with HP. The frequency of this infection had no statistically significant correlation with the underlying cause of dyspepsia as determined by endoscopy. In other words, there was no difference in the prevalence of HP in patients with PUD and NUD. These observations are consistent with those reported previously for other ethnic populations.[17-19] Moreover, the severity of symptoms had little correlation with the HP status of patients. Other investigators have reported similar findings.[20-23]

Only a minority of our patients (11.5%) were found to have bona fide duodenal ulcers. Interestingly, no gastric ulcers or gastric cancers were encountered in this group of patients, despite the high prevalence of HP in our population. Instead, most patients had NUD. Alarm symptoms, such as weight loss and nocturnal pain, did not predict the presence of PUD. The prevalence of HP also appeared to be high across the socioeconomic boundaries. This apparent lack of association between the prevalence of HP on one hand and the symptoms and cause of dyspepsia on the other hand most probably reflects the high frequency of HP in the general population.

Since the benefit of eradicating HP in patients with NUD is uncertain and is currently not recommended by most authorities,[24] it would be unwise and possibly not cost effective to treat HP in dyspeptic patients without establishing a positive diagnosis of PUD. Moreover, EGD is an important tool in excluding other upper gastrointestinal disorders, such as gastroesophageal reflux and celiac disease. Finally, an EGD reassures patients with NUD that their stomach is normal.

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CYTOGENETIC EVALUATION OF 1000 CASES OF CHORIONIC VILLUS SAMPLING

M. Anwar Iqbal, PhD, FACMG; Gene F. Manko, MD; Jay Trabin, MD;
Carole Virelles, VS; Laird Jackson, MD, FACMG

Background: Chorionic villus sampling (CVS) is used routinely as a first trimester diagnostic procedure for fetal karyotyping in at-risk pregnancies. The success of the procedure is dependent on the experience of the operator performing it. The objective of this study was to determine the relationship between an operator-controlled clinical and laboratory setting and the safety and reliability of CVS service.
Patients and Methods: One thousand patients had a CVS procedure for a variety of indications, such as advanced maternal age, previous child with chromosome abnormality, etc. Both transcervical and transabdominal procedures were performed, according to placental location and uterine environment. For cytogenetic diagnosis, direct and short-term cultures were set up according to standard laboratory protocol.
Result: Cytogenetic results were obtained in 99.6% of studies with 94.5% normal (46,XX or 46,XY), with the remaining having a variety of numerical and structural chromosomal abnormalities. Maternal cell contamination was found in 2% of the first 262 cases, while the overall rate observed in the 1000 samples was 0.5%. Level II mosaicism was observed in 0.8% and level III mosaicism observed in 0.9% of cases, respectively. The overall rate of pregnancy loss of chromosomally normal pregnancies within 28 weeks of gestation was 2.8%. No limb reduction defects were seen in any infant post-CVS.
Conclusion: Our record demonstrates that experienced operators can deliver a safe and reliable CVS service.
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Key Words: Chorionic villus sampling, karyotypes.

Chorionic villus sampling (CVS) for first trimester fetal karyotyping is now a routine diagnostic procedure in at-risk pregnancies. A number of large collaborative studies throughout the world have documented the safety of the CVS procedure.[1-5] However, Ledbetter et al.[3] observed a nonsignificant increase of 0.5% to 0.8% in pregnancy loss rate in the CVS group compared to the amniccentesis group.[3] Contradictory findings of limb reduction associated with CVS have also been reported.[6-9] Based on the current data, it has been determined that CVS performed after 10 weeks of gestation, in the first trimester, is a safe, accurate and reliable prenatal test for detecting cytogenetic abnormalities.[10]

In the present study, we report our experience of 1000 CVS procedures performed in an operator-controlled clinical and laboratory setting. There were only two operators who performed the CVS procedures throughout this study, with a single ultrasonographer. The CVS specimens were processed in the laboratory by the same small staff throughout the study.

Patients and Methods

Patient Preparation

Prior to the physician entering the room, an initial ultrasound scan confirms fetal viability and number, gestational age and placental location, and assesses the uterine environment for the presence of any structural factors which may interfere with the procedure. The patient is asked not to void, so that the fluid in the bladder may be used as an angling tool for the position of the

TABLE 1. *Summary of 1000 CVS procedures performed at the Genetic Institute of Florida (GIF).*

				Total pregnancy loss		
Total CVS	TA	TC	CVS failed	SAB	TAB	Follow-up obtained
1000	446 (44.6%)	554 (55.4%)	2: no sample (0.20%); 2: no growth (0.20%)	28 (2.8%)	27 (2.7%)	1000

TA=transabdominal; TC=transcervical; SAB=spontaneous abortion; TAB= therapeutic abortion.

From the Genetics Institute of Florida (Drs. Iqbal, Manko, Trabin and Virelles), West Palm Beach, Florida, and the Jefferson Medical College (Dr. Jackson), Philadelphia, USA.

Address reprint requests and correspondence to Dr. Iqbal: Head, Cytogenetics/Molecular Genetics Section, Department of Pathology and Laboratory Medicine, MBC 10, King Faisal Specialist Hospital and Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia.

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E-mail: iqbal@kfshrc.edu.sa.

placenta. The route of access for the CVS procedure, i.e., transcervical or transabdominal, may be influenced by the presence of pathogens, such as gonorrhea, chlamidia, and active herpes. In such cases, the transabdominal approach is done by using a 19 gauge, 3 1/2" needle that has been prepared with a heparin solution to prevent clogging. The total biopsy time is 5-7 seconds. With a transcervical CVS, a special Trophocan CVS catheter (26 cm) made by Portex is used, with an approximate sampling time of 10-12 seconds. Throughout the entire procedure, ultrasound visualization is constant. For the technically difficult procedure, certain efforts were employed to alter the placental angle. The most common method used in this study was to change the volume of urine in the patient's bladder to make the angle more favorable, and myometrial contractions were used to advantage to reshape the uterine wall behind the placenta. These may occur every 20-30 minutes. When a cervical CVS is preferred and if the initial angle is too steep for a smooth insertion of the catheter, a tenaculum may be used to grasp and gently pull the cervix in order to straighten the uterus. Maneuvering the speculum may also enhance the angle of entry. In cases where a cervical CVS is contraindicated and uterine or placental position are not optimal for an abdominal approach, digital manipulation of the uterus can be helpful in holding it in a more suitable position for the catheter.

After the CVS was successfully completed, the uterine environment was again assessed for the presence of any placental separation or hemorrhage. The fetal heartbeat was reconfirmed. The patients' tolerance was usually very good, with a majority of the patients able to leave immediately with few restrictions. Information on the outcome of the pregnancy was obtained on 95% of the patients from a questionnaire which was sent to the referring physician before the expected delivery date, or by telephone contact if this was not returned. Data was collected on fetal sex, birthweight, and congenital malformations. Statistical comparisons were made by chi-squared test, and a *P*-value of less than 0.05 was considered significant.

Laboratory Procedure

As a general laboratory policy, 20 mg or more of chorionic villi were requested, however, smaller amounts (2 mg-5 mg) were also processed. As soon as the sample was received in the laboratory, the villi were separated meticulously from the maternal decidua under a stereomicroscope. After separation, villi were processed for both direct (24-48 hours) and short-term (5-8 days) culture analysis, using a standard laboratory procedure. Briefly, for direct analysis, one-third of the villus sample was transferred into a 35-mm sterile Petri dish containing 3 mL of 50:50 mixture of Chang and Ham's F12 complete media with 1-2 drops of colcemid from a 22-gauge needle (stock conc. 10 μg/mL). The villi were incubated for 24-48 hrs at 37°C in a 5% CO_2 and 5% O_2 environment. At harvest, the villi were treated with prewarmed 1% sodium citrate hypotonic solution for 20 minutes at 37°C. The villi were then fixed in a 3:1 methanol acetic acid mixture. After the fixation, the villi were dissociated by a chilled 1:1 aqueous acetic acid solution and slides were prepared by a modification of Simoni et al.[11] The villus cell suspension was spread with a bent Pasteur pipette on a clean slide left at 37°C. The slides were aged at 60°C for one to several days and subsequently GTG-banded for chromosome analysis. A minimum of 4-10 metaphases

TABLE 2. *Individual operator's performance in the outcome of CVS.*

Operator	CVS performed	Post-CVS loss	*P*-value	Post-CVS loss with >1 insertion	*P*-value
A	295	12 (4.06%)		4 (33.3%)	
B	295	7 (2.37%)	0.24	1 (14.28%)	0.35
B	Next 410	6 (1.21%)			

TABLE 3. *Number of post-CVS pregnancy losses in 1000 samples.*

Case TA/TC	Gestation age	Result	Loss
7 TC/TC (twins)	11W4D	46,XY; 46,XY	SAB 20W
33 TC	11W	46,XX	Miscarriage 18W
74 TC	10W6D	46,XY	IUFD 27W
135 TC	10W	46,XY	Miscarriage 15W
166 TC	9W1D	46,XY	IUFD 21W
201 TC/TC (twins)	10W5D	46,XX; 46,XY	SAB 16W
208 TC	10W4D	46,XY	PROM 17W
218 TA/TC (twins)	10W6D	46,XX; 46,XY	PROM 23W
317 TC	9W4D	47,XY, +21	Miscarriage post-procedure
332 TA	11W6D	47,XX, +21	Miscarriage 18W
375 TA	9W6D	46,XY	IUFD 20W
443 TC	9W1D	46,XX	SAB 17W
566 TA	10W5D	46,XY	IUFD 17W
852 TC	10W6D	46,XX	IUFD 16W
34 TC	10W	46,XY	14W
78 TC	9W6D	46,XY	12W6D
86 TC	9W6D	46,XX	11W6D
211 TA	11W1D	46,XY	15W1D
216 TC	10W	46,XY	13W
290 TC	9W4D	46,XX/47,XX, +13	12W4D
779 TC	9W	47,XX, +18	10W
803 TC	9W5D	46,XY	13W?
887 TA	11W1D	46,XY	13W1D
911 TA	9W4D	46,XY	13W1D
931 TA	9W6D	46,XX, t(8;10)	13W6D
1046 TA	11W4D	46,XY/47,XY, +21	12W4D
1005 TA	10D	46,XX	15W

TC=transcervical; TA=transabdominal; PROM=premature rupture of the membrane; SAB=spontaneous abortion; IUFD=intrauterine fetal death; W= weeks; D-days.

TABLE 4. *Mosaic and non-mosaic chromosome abnormalities observed in 1000 CVS samples.*

Cytogenetic diagnosis	Total
Normal	949
Numerical abnormality	
Autosomal aneuploidy	
47,XX or XY, +21	14
47,XX or XY, +18	7
47,XX, +13	1
47,XY, +14	1
47,XY, +16	1
47,XX, +2	1
46,XY/47,XY, +21	1
46,XY/47,XX, +18	1
46,XX/47,XX, +13	1
46,XY/47,XY, +7	1
46,XY/47,XY, +5	1
46,XY/47,XY, +10	1
69,XXX	1
Sex chromosome aneuploidy	
47,XXY	1
45,X/46,XY	2
45,X/46,XX	1
46,XY/47,XYY	1
47,XXY, t(3;5) (q22; q13) mat	1
Structural abnormality	
Balanced	
45,XY, der (13;15) (q10; q10)	1
45,XX, der (15;22) (q10; q10)	1
45,XX, der (14;21) (q10; q10)	1
46,XX, t(8;10) (q24; q24) mat	1
46, XX, t(12;17) (p12; q21) pat	1
Unbalanced	1
46,XX, der (21;21) (q10;10) +21	1
46,XY, der (8) t(8;10) (q24; q24) mat	1
46,XX, der (13) t(3;13) (q29; q22) mat	1
46,XX, add (18) (p11.3)	1
46,XX, del (10) (p15)	1
46,X, del (X) (p22)	1
46,XX/47,XX, i(12p)	1
46,XX/47,XX, +mar	1
Total	1000

were analyzed. The direct cultures were used to detect maternal cell contamination, confined placental mosaicism (CPM), and uniparental disomy (UPD).

For short-term cultures, cleaned pooled villi were incubated for 1 hour at 37°C in 1X Trypsin-EDTA solution, followed by a brief wash in HBSS and then incubated in collagenase solution (80-100 U/mL) for 45-60 minutes at 37°C. A minimum of 6-8 coverslips were set up on each sample in 100% Chang media, and a back-up flask was maintained until the case was completed. For cytogenetic diagnosis, 15-20 metaphases were analyzed with the routine GTG-banding technique. To differentiate between levels I, II, and III mosaicism, standard protocol used in amniotic fluid culture analysis was adopted.[12] Briefly, three levels of mosaicism are defined: Level I: a single abnormal cell in a coverslip; Level II: two or more cells with the same chromosome abnormality in a single coverslip; Level III: two or more cells with the same chromosome abnormality found in multiple coverslips. For normal and abnormal karyotypic designations, the International System for Human Cytogenetic Nomenclature (ISCN) was followed.[13]

Results

Sampling Technique

Out of 1000 patients choosing CVS, 86.7% had the procedure for advanced maternal age; 6.6% were referred for a previous child with abnormal chromosome; 3.1% for maternal anxiety. The remaining 3.6% of patients had CVS for various reasons: translocation carrier (0.6%); recurrent abortion (0.5%); family history of mental retardation (0.8%); paternity testing (0.2%); teratogen exposure (0.2%); metabolic disorders (1.3%).

A successful sample was obtained in 996 patients (99.6%). A total of 446 patients (37.47%) underwent transabdominal CVS, while 554 patients (55.4%) underwent transcervical procedure (Table 1). Eleven patients (1.1%) had a second prenatal diagnostic procedure, either due to culture failure or mosaicism, 28 patients (2.8%) had spontaneous losses within 28 weeks of gestation, and 27 cases (2.7%) had a therapeutic abortion due to chromosomal abnormality. Table 2 gives the data on the spontaneous losses, which were mainly due to operator's inexperience. Table 3 summarizes the post-CVS pregnancy loss. Follow-up information after delivery of the child was obtained for 95% of patients. There were no recorded cases of limb reduction deformities in our population.

Cytogenetic Diagnosis

1) Numerical and Structural Abnormalities: Normal chromosome results were obtained in 949 cases (94.9%). Table 4 summarizes both mosaic and non-mosaic chromosome abnormalities observed in 51 CVS cases (5.1%). Trisomy 16 was observed in one CVS sample, although follow-up amniocentesis revealed a normal chromosomal result with a normal outcome at delivery. In many cases, confirmation studies were performed on the abortus material, with no false-positives observed.

2) Level II and Level III Mosaicism: A total of nine cases out of 1000 samples were observed to show level III mosaicism of both autosomes and sex chromosomes. The results of level III mosaicism are summarized in Table 5. Two of these cases (C41 and C803), one with trisomy 13 and one with trisomy 21 mosaicism, either miscarried or resulted in fetal demise. One case of trisomy 7 mosaicism opted for therapeutic abortion despite reassurance of CPM. In the remaining two cases, one with trisomy 20 and the other with XYY mosaicism, follow-up amniocentesis was not recommended. Both of these cases had a normal outcome at the time of delivery. Table 6 summarizes data on the level II mosaicism observed in eight of 1000 cases (0.8%). In five of these cases, a follow-up amniocentesis was recommended and the chromosome result in these cases were normal. The pregnancy outcome was also normal in the cases. In two cases of level II mosaics (C793

and C819) follow-up, amniocentesis was not recommended, due to strong suspicion of CPM. Both of these cases had a normal liveborn outcome.

3) Maternal Cell Contamination: Maternal cell contamination (MCC) occurred five times in the first 262 cases, and has not been encountered in the last 738 cases analyzed (0.5% overall). In four of these cases, only a single XX cell was found in XY analysis. Since MCC could not be detected in female fetuses, the overall rate would be twice the rate (0.5%) observed in the male fetuses, i.e., 1.0%.

TABLE 5. *CVS cases with level III mosaicism.*

Case #	Cytogenetic result	Follow-up amnio	Outcome
C41	46,XX/47,XX, +13	–	Miscarriage 4 weeks post-CVS
C204	46,XY/47,XY, +7	–	TAB
C214	45,X/46,XY	113 cells 46,XY	Normal male
C188	46,XY/47,XY, +5	53 cells 46,XY	Normal male
C233	46,XY/47,XY, +10	43 cells 46,XY	Normal male
C226	46,XY (long-term culture) 47,XY +20/48,XY, +20, +mar (direct culture)	Not recommended	Normal male
C475	46,XY/47,XYY	Not recommended	Normal male
C803	46,XY/47,XY, +21	–	IUFD 4 weeks post-CVS
C558	45,X/46,XY	23 cells 46,XY	Normal male

TABLE 6. *CVS cases with level II mosaicism.*

Case #	Cytogenetic result	Follow-up amnio	Outcome
C208	46,XX/47,XX, +13	42 cells 46,XX	Normal female
C514	46,XX/47,XX, +22	54 cells 46,XX	Normal female
C637	45,X/46,XY	20 cells 46,XY	Normal male
C665	45,XX, -19/46,XX	–	Miscarriage
C793	46,XX/46,XX, der (2) t(2;?)	Not recommended	Normal female
C819	45,X/46,XX/47,XXX	Not recommended	Normal female
C146	45,X/46,XX	47 cells 46,XX	Normal female
C779	46,XX/47,XX, +18	31 cells 46,XX	Normal female

Discussion

Chorionic villus sampling was performed either transcervically or transabdominally in 1000 patients by two operators. The low pregnancy loss rate (2.3%) and a high culture success rate (99.6%) in our study is attributed to the coordination between the ultrasonographer, the operator and the laboratory staff.

A total of 28 out of 1000 patients (2.8%) who had CVS lost their pregnancy within 28 weeks of the procedure. These losses consisted of both normal and abnormal chromosome fetuses. Obstetrical problems, such as incompetent cervix, bicornuate uterus, and/or malignant hypertension in some of the patients in this group, may have played a role in spontaneous loss. The loss rate observed in this study is lower than the average loss rate of about 4% cited for CVS.[8] We did not observe any relationship between the loss rate and type of procedure (TA vs. TC).

The authors have observed that the learning curve for each individual physician was different, given the same use of ultrasound instrumentation, ultrasound technician, and the same training protocol for CVS sampling. The training protocol for CVS sampling required each physician to perform CVS on 50 non-continuing pregnancies. The differences observed between the two operators in our study with regard to procedure-related losses clearly indicates that the CVS procedure requires high technical skills. Although the authors failed to observe the difference as statistically significant, our data indicates that lack of high technical skills in CVS sampling may ultimately reflect on factors such as post-procedure loss, number of passes to obtain sufficient sample, sample size and repeat procedure. The importance of a technically skilled operator in the success rate of CVS was also recently addressed in other studies.[14-16]

The cytogenetic analysis success rate of 99.6% obtained in the first attempt is comparable to other reports.[3] Through repeat CVS of failed samplings, the success rate reached 100%. One case of full trisomy 16 without any normal cells was observed, which turned out to be a false-positive. The follow-up amniocentesis in this case showed a normal chromosomal result with a normal liveborn child without intra-uterine growth retardation (IUGR). This was clearly a case of CPM with a selective advantage of trisomy 16 cells in vitro. Rare trisomies, such as trisomy 7, 10 and 5, still pose a problem in CVS, although follow-up amniocentesis in such cases has revealed a normal result, proving that such trisomies are mainly confined to placenta. Studies of placental mosaicism and their pregnancy outcome are ongoing to classify these relationships.[17-20]

The incidence of level II and III mosaicism in our study was comparable to that reported in other large CVS collaborative studies.[3-4] Although the incidence of level III mosaicism was much higher than in amniocentesis (0.9% vs. 0.25%), the follow-up normal result with a normal outcome in all 13 cases in our study is reassuring that many of the low-level III mosaic findings in CVS are most likely due to CPM. Nevertheless, follow-up amniocentesis should be recommended in level III mosaic findings in CVS, irrespective of their percentage in the analysis. In our sample, MCC was found to be much lower (0.5%) than reported in other studies,[3,20-22] and the low rate of MCC was independent of the procedure, TA vs. TC. We believe that the laboratory procedure for cleaning the villi is an important factor in low MCC rather than the type of sampling technique, as is suggested in other reports.[3] However, direct CVS culture analysis can be utilized on all adequate CVS samples to confirm the XX result on cultured villi.

In conclusion, the cytogenetic analysis of 1000 CVS samples in the present study reiterates that CVS is a safe, accurate and reliable first trimester technique for prenatal diagnosis in high-risk pregnancies. The success of the CVS is directly related to the experience of the operator and the laboratory handling of the sample.

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ASSESSMENT OF INDICATORS FOR PREDICTING CHOLEDOCHOLITHIASIS BEFORE LAPAROSCOPIC CHOLECYSTECTOMY

Mohammed K. Alam, FRCS

Background: The objective of this report was to study the sensitivity of indicators used for predicting bile duct stones and their endoscopic removal before laparoscopic cholecystectomy.

Patients and Methods: A retrospective study was conducted on 104 patients who successfully underwent endoscopic retrograde cholangiopancreatogram (ERCP) before laparoscopic cholecystectomy at Riyadh Medical Complex between 1992 and 1994 (1412H-1414H). Six indicators—jaundice, biliary pancreatitis, stones in bile duct on sonography, dilated bile duct (>7 mm) on ultrasonography, dilated bile duct with deranged liver function test, and deranged liver function test without jaundice—were used for suspecting choledocholithiasis and endoscopic removal before laparoscopic cholecystectomy.

Results: Ultrasound correctly predicted bile duct stone in 75%, followed by dilated bile duct with deranged liver function test (46%). Clinical jaundice and biliary pancreatitis were equally sensitive indicators (42% each). Sensitivity of only dilated bile duct on ultrasonography in predicting duct stone was 36%. Deranged liver function without jaundice was the least sensitive (22%) of the predictors. Overall, these indicators correctly diagnosed bile duct stones in 34% of patients.

Conclusion: Until laparoscopic exploration of bile duct or a noninvasive technique, such as magnetic resonance cholangiopancreatogram (MRCP), is widely available, these predictors will help in selecting patients with bile duct stones for preoperative removal. Other workers have suggested combining these indicators to improve the predictive value.

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Key Words: Choledocholithiasis, laparoscopic cholecystectomy.

Laparoscopic cholecystectomy has rapidly become the procedure of choice for symptomatic gallstone disease. This has led to a fundamental change in the management of common bile duct stones. During the prelaparoscopic era, biliary duct stones and cholelithiasis were managed during the same operation, using intraoperative cholangiogram and common bile duct exploration. The laparoscopic exploration of choledocholithiasis, although available, is limited to a few centers, due to limited experience with this demanding technique.[1-4] Therefore, until the laparoscopic manipulation of bile duct is widely available, surgeons have relied on the endoscopic retrograde cholangiopancreatography (ERCP) and sphincterotomy for preoperative clearance of common bile duct stones.

Clinical, biochemical and sonographic criteria have been used to predict the presence of duct stones.[5] Since the introduction of laparoscopic cholecystectomy in our hospital, a similar policy of preoperative ERCP in patients with suspected bile duct stones has been adopted. This retrospective study was undertaken to evaluate the sensitivity of indicators used for predicting duct stones and endoscopic removal before laparoscopic cholecystectomy, and suggests ways to improve the selection criteria for identification of choledocholithiasis.

Patients and Methods

The medical records of consecutive patients who had laparoscopic cholecystectomy or attempted laparoscopic cholecystectomy and subsequently converted to open cholecystectomy during the three-year period 1992-1994 (1412H-1414H) at Riyadh Medical Complex (RMC) were retrieved. Patients who were directly submitted to open cholecystectomy were not included in the study. From these records, those who were referred for ERCP and endoscopic removal of suspected bile duct stones were selected for analysis. The data collected on these patients included age, sex, mode of presentation, biochemical profile, sonographic findings, ERCP findings and complications related to this procedure. Analysis of this data formed the basis of this report.

From the Department of Surgery, Riyadh Medical Complex, Riyadh, Saudi Arabia.

Address reprint requests and correspondence to Dr. Alam: Department of Surgery, King Khalid University Hospital, P.O. Box 7805, Riyadh 11472, Saudi Arabia.

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TABLE 1. *Patient groups according to the indicators used for preoperative ERCP and their findings (n=104).*

Indicators	Findings
Bile duct stones on ultrasonography (n=4)	Stones removed in 3 patients (75%)
Dilated bile duct on ultrasonography (>7 mm) + deranged LFTs (n=13)	Stones removed in 6 patients (46%)
Acute pancreatitis (n=12)	Stones removed in 5 patients (42%)
Clinical jaundice (n=12)	Stones removed in 5 patients (42%)
Dilated bile duct on sonography (>7 mm) (n=14)	Stones removed in 5 patients (36%)
Deranged LFTs (n=49), elevated alkaline phosphatase, SGOT, SGPT	Stones removed in 11 patients (22%)

LFT=liver function test; SGOT=serum glutamic oxaloacetic transaminase; SGPT=serum glutamate pyruvate transaminase.

All patients had full clinical examination, blood counts, biochemical analysis, including serum amylase estimation when indicated, and abdominal ultrasound examination. Patients were grouped according to the six indicators used for suspecting bile duct stones: 1) biliary pancreatitis—serum amylase >1000 IU/L on admission; 2) jaundice, clinically and biochemically; 3) dilated bile duct (>7 mm) on ultrasonography; 4) stones in bile duct on sonography; 5) deranged liver function (elevated alkaline phosphatase, SGOT, SGPT) test in the absence of clinical jaundice; and 6) dilated bile duct (>7 mm) on sonography with deranged liver function.

Results

During the three-year period, 753 patients were submitted for laparoscopic cholecystectomy. One hundred and eight (14%) of them were suspected to have biliary duct stones. They were submitted to preoperative ERCP for removal of duct stones. Successful cannulation was achieved in 104 patients (all the data given below relates to this group of patients). The ages of the patients ranged between 16 and 80 years (mean, 39.7), with the majority of them being female (78 patients, 75%). Table 1 presents the patient groups divided into indications and ERCP findings. Ultrasound-detected biliary duct stones had the best predictive value (n=4, 75%), followed by ultrasonographically detected dilatation of bile duct with deranged liver function (n=13, 46%). Stones were recovered from biliary tree in 42% each of patients presenting with biliary pancreatitis (n=12) and clinical jaundice (n=12). Ultrasound-detected biliary dilatation without derangement of liver function correctly predicted biliary duct stones in only 36% (n=14) of patients. Deranged liver functions test alone was the least sensitive indicator (n=49, 22%). Overall, stone recovery rate was 34% (n=35). One patient required two sessions to clear the common duct of all stones. Other abnormalities detected in 11 patients (10.5%) were papillitis (n=6), pancreatic divisum (n=2), papillary stenosis (n=1), Mirizzi's syndrome type I (n=1), and low insertion of cystic duct (n=1). Only one patient (0.9%) developed mild pancreatitis following ERCP. There was no mortality in the study group.

Discussion

Associated choledocholithiasis is present in 10%-15% of patients undergoing cholecystectomy.[6] This incidence rises with age and the duration of gallstone symptoms.[7,8] The increasing incidence of biliary duct stones with age was also noticed in our patients, except for the 50-59-year age group, for which no satisfactory explanation could be found.

Bile duct stones are associated with a high rate of severe complication,[9] such as cholangitis or pancreatitis. Therefore, they should always be removed. Since laparoscopic cholecystectomy has become the treatment of choice for symptomatic gallstone disease, the best clinical strategy to deal with choledocholithiasis is under debate.[10] Early reported results of laparoscopic choledocholithotomy are encouraging, but its availability is limited to a few centers.[1-3] This has resulted in an increasing trend in the use of ERCP to deal with bile duct stones. However, the controversy regarding its optimum timing, either before or after laparoscopic cholecystectomy, has not yet been settled.[11,12] Postoperative ERCP has been preferred by a few authors because it minimizes the cost and reduces morbidity.[11] The only drawback in this policy is that if ERCP is unsuccessful, it will lead to another operation. On the other hand, routine use of preoperative ERCP has been recommended,[13,14] but this has not received wide acceptance due to high cost and morbidity.

A widely adopted policy has been to select patients at risk for biliary duct stones for preoperative ERCP and bile duct clearance.[15-17] The criteria for selection have been based on clinical, biochemical and sonographic findings.[5,15-17] There has been renewed interest in intravenous cholangiography for detection of bile duct stones as newer contrast materials which are less allergenic and provide adequate imaging become available.[18] Magnetic resonance cholangiography is another new modality being used in the assessment of biliary tract disease. Preliminary results of MRCP are similar to those of more invasive ERCP,[19] but this imaging is not yet widely available.

Clinical jaundice, acute biliary pancreatitis, deranged liver functions, and dilated common bile duct or presence of stones in biliary tree on ultrasonography were used in this study as predictors of choledocholithiasis. They correctly predicted stones in bile ducts in 35 patients (34%). Other studies using very similar indicators[8] have reported stone detection rates of 32%-44%.[15,20,21]

Ultrasonography was the single most sensitive indicator, whereas deranged liver function tests in the absence of clinical jaundice alone were the least sensitive criteria in the present study. Although most patients of gallstone-associated pancreatitis have been described to pass stones in the duodenum,[22] in this study, stones were recovered in 42% of patients with biliary pancreatitis. Others have also reported a yield of 37%-42% by ERCP in biliary pancreatitis.[21,23] This supports the view that preoperative ERCP may be beneficial in these cases.[21] Other abnormalities of biliary pancreatic duct were detected by preoperative ERCP in 11 patients (10.5%). Overall, the indicators used in this study correctly predicted abnormalities in 46 patients (44%).

One may contend that 58 patients (56%) with normal ERCP in the present series had to go through unnecessary discomfort and risk with preoperative ERCP. This could have been reduced by using strict predictive criteria. The use of an optimal model, by combining the predictive factors such as age, clinical jaundice, elevated alkaline phosphatase (ALP) and alanine aminotransferase (ALT), dilated CBD or presence of stones in biliary tree on sonography, will improve the sensitivity and patient selection for preoperative ERCP.[16,17] The added advantage of preoperative ERCP may be the knowledge of biliary tree abnormalities which might prevent the bile duct injuries.

In summary, stones detected by ultrasonography in bile duct, dilated bile duct with deranged liver function tests, clinical jaundice and recent attack of biliary pancreatitis, were found to be sensitive predictors of bile duct stone in this study. However, the selection of patients at risks for CBD stones can be improved by combining these clinical, biochemical and sonographic indicators as a model. Until laparoscopic choledocholithotomy is widely available, such patients can be safely managed by endoscopic removal of these stones before laparoscopic cholecystectomy.

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COARCTATION OF THE AORTA: A CALL FOR EARLY DETECTION

Sameeh S. Ghazal, MBBS, DCH, MRCP; Maged M. El Samady, MBBCh, MRCP;
Mansour Al Howasi, MBBS, DCH, FRCP; Sulaiman Musallam, MBBS, DCH

Background: Early repair of coarctation of the aorta (COA) is associated with few perioperative complications and better long-term outcome. Therefore, early detection and treatment of COA patients is extremely desirable. The aim of this study was to review our referral system, the effectiveness of neonatal screening examination, and orient physicians about this abnormality, the mode and age of presentation, differences in presentation between cases with isolated COA, and cases associated with other cardiac lesions.
Patients and Methods: This was a retrospective study of 61 inpatients admitted to our hospital between January 1989 and December 1996, who were found to have COA. Referral data was analyzed and compared to hospital cardiac evaluation findings.
Results: All the patients were referred after being symptomatic, but there was no suspicion of COA in any of the cases. One of the patients was referred by a pediatrician from a private clinic, and the rest by hospital pediatricians. Femoral pulse and cardiac murmur were commented upon in only three of the referral letters. Systolic pressure gradient (SPG) between upper and lower limbs and systolic hypertension were not commented on in any of the referral letters. SPG ≥10 mm Hg and systolic hypertension were found in 100% and 58% of the patients, respectively, upon evaluation in our center. SPG in patients with COA associated with other cardiac lesions was significantly lower than in patients with isolated COA (P=0.02).
Conclusion: Increased awareness in our primary health physicians of the importance of the neonatal screening examination and of measuring blood pressure in the limbs to detect COA early is needed. Timing of the neonatal screening examination between the third day and the third week is recommended. Systolic pressure gradient is a reliable method to detect COA, and in the lower significant range (≥10 mm Hg) is associated with complex cardiac lesion rather than isolated COA.
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Key Words: Coarctation of the aorta, femoral pulses, neonatal screening examination.

Congenital heart malformations are the most common of all congenital malformations, accounting for 9% of all infant deaths and 40% of deaths within this group.[1] Left ventricular outflow tract obstruction (LVOTO) occurs in 6/10,000 live births, or 7% of patients with congenital heart disease (CHD).[2,3] Detection of coarctation of the aorta (COA) prior to the onset of symptoms should result in earlier referral, lower perioperative morbidity and mortality, and better long-term outcome.[4-7]

Screening for CHD is one of the main reasons for routine examination of babies in the neonatal period and in early infancy.[8,9] It has long been recognized that weak or absent femoral pulse, upper limb hypertension and systolic pressure gradient (SPG) between upper and lower limbs are sensitive screening indicators for COA.[10,11] Unfortunately, CHD may escape detection in the neonatal and six-week period examinations, especially if they are not properly performed.[1]

Patients and Methods

The records of patients admitted to Suleimania Children's Hospital (SCH) between January 1989 and December 1996 were reviewed, and 66 patients with the diagnosis of LVOTO were found. Three patients with hypoplastic left heart and two with interrupted aortic arch were excluded from the study. Sixty-one patients with COA with or without associated cardiac lesions were accepted into the study. Patients seen and diagnosed as outpatients were not included.

Data recorded included age, sex, cause of referral, position of referring physicians, and clinical signs (femoral pulse, blood pressure, and cardiac murmur). Data collected from referral letters were compared with data documented in the files by our cardiologist.

The patients were classified into two groups. The first group was made up of patients with isolated COA (16/61,

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From the Department of Pediatrics, Suleimania Children's Hospital, Riyadh, Saudi Arabia.

Address reprint requests and correspondence to Dr. Ghazal: Department of Pediatrics, Suleimania Children's Hospital, P.O. Box 59046, Riyadh 11525, Saudi Arabia.

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26%), and the second group of patients had COA associated with other cardiac lesions (45/61, 74%).

Blood pressure (B/P) readings were considered correct if measured in the four limbs in the same sitting by oscillometric methods and clearly documented in the file. This was done in 38 patients. The B/P readings of 23 patients were excluded, since they were not clearly recorded, and those of three patients measured in less than three limbs and those measured manually and not by oscillometric methods were also excluded. Echocardiography machines used included two Toshiba models, both with color flow and Doppler. As cardiac catheterization and surgery are not available in our center, it was not possible to include the data in this study. *T*-test was used to test the difference between the means, while chi-squared and Fisher's exact tests were used to test the difference between qualitative data when appropriate.

Results

A total of 66 cases were admitted as left ventricular outflow tract obstruction. Five patients were excluded from the study. The study was performed on 61 patients with coarctation of the aorta (COA). Of these, 37 were male and 24 were female, with male to female ratio 1.5:1. The mean age of presentation was 54.8 days (SD 61 days) with a range of 2-355 days. Thirty-one patients (51%) presented during the first month of life, and 30 patients (49%) presented between one month and 12 months of age. Data on the age at presentation is shown in Table 1. The causes for referral were as follows (Table 2): breathlessness in 19 patients (31%); cyanosis in 18 patients (30%); heart failure in nine patients (15%); abnormal femoral pulse in three patients (5%); and cardiac murmur in two patients (3%). The remaining 10 patients (16%) were referred for nonspecific complaints. BP was not recorded in any of the referral letters, so it is likely that hypertension and systolic pressure gradient were not detected in any of the patients by the referring physicians.

None of the patients was referred with the provisional diagnosis of COA. Findings detected by the referring physicians compared with findings of the cardiologist are shown in Table 3. Our patients with coarctation and associated cardiac lesions (group B) presented earlier (mode of 30 days) than patients with isolated coarctation (group A, with mode of 105 days) (Table 1), but the difference was not statistically significant (*P*=0.72). There was no statistical significance between group A and group B regarding characters of femoral pulse (*P*=0.56). Of the 38 patients with correct blood pressure measurement, 22 patients (58%) were found to have systolic hypertension when their BP was plotted in a standard BP percentile chart (Table 4). All patients with correct BP measurements had systolic pressure gradient (SPG) between upper and lower limbs of 10 mm Hg or more (Table 5). The mean SPG in all patients was 51 mm Hg (39.9). The mean SPG in patients in group B was 39.1 mm Hg (31.2), which was significantly lower (*P*=0.02) than the mean SPG in group A, which was 69.1 mm Hg (45.7) (Table 5). In group B, ventricular septal defect (VSD) and patent ductus arteriosus (PDA), either as single or combined lesions, were the most common associated cardiac lesions (35/45 patients, 78%).

TABLE 1. *Age data on presentation (days).*

	Group A (%)	Group B (%)	*P*-value
Number	16/61 (26)	45/61 (74)	
Mean	56.9	53.8	0.72
SD	89.9	49.1	
Mode	105	30	
Median	15	45	
Minimum	2	4	
Maximum	355	240	
≤1 month	11/16 (69)	20/45 (44.5)	
1 month-1 year	5/16 (31)	25/45 (55.5)	

Group A: patients with isolated COA; group B: patients with COA associated with other cardiac lesions.

TABLE 2. *Cause of referral for cardiac consultation.*

	Number (%)
Breathlessness	19 (31)
Cyanosis	18 (30)
Heart failure	9 (15)
Abnormal femoral pulse	3 (5)
Cardiac murmur	2 (3)
Nonspecific	10 (16)

Discussion

Many studies have indicated that delayed repair of COA is associated with an increased morbidity and mortality because of cardiovascular diseases in adult life.[4-6,12-18] Furthermore, it has been stated that repair during early childhood is associated with less systemic hypertension and improved long-term outcome.[4-7] Therefore, early identification and repair of this lesion is highly desirable. Fifty-one percent of our patients presented below the age of one month, which reflects the time of onset of symptoms, and thus the severity of their lesions,[6,15] rather than successful detection in neonatal screening examination, as none of them was asymptomatic at the time of referral.

None of the referring physicians documented SPG or even BP in the referral letters (Table 3). This reflects failure of our neonatal screening examinations to detect important diseases like COA. One reason for missing such abnormalities may be early newborn discharge (within 24-48 hours after delivery). It has been mentioned in a study by Ward et al.[15] and others[19,20] that cardiac symptoms may not develop before 48 hours of age, and that most infants with COA should have detectable physical signs (hypertension and/or abnormal femoral pulse) by five days of age (i.e., after discharge), and that almost 50% will develop severe symptoms prior to 14 days of age (i.e., before the first vaccination visit). So re-examination of newborn between three days and two weeks of age should become mandatory. Another reason is the non-recognition of signs and symptoms of coarctation in the young infant, especially in the first 24 hours, when the ductus arteriosus is still patent.[15] A third reason may be a lack of familiarity on the part of the physicians about this abnormality and its manifestation. At the time our patients were referred, 77% had cardiac murmur. Of the 38 patients with correct B/P reading, 58% had systolic hypertension, and all patients had SPG ≥10 mm Hg. The referring physicians did not detect most of these signs (Table 3). A fourth reason could be the low sensitivity (31%) of the present neonatal screening examination.[1] The results of our study suggest that all of these factors play a role in delaying the detection of abnormalities.

TABLE 3. *Comparison between clinical findings in the referral letters and the cardiologist's report.*

	Referring physician	Hospital cardiologist
Femoral pulse		
Absent	0	6 (14%)
Weak	3 (5%)	33 (75%)
Normal	0	5 (11%)
No comment	58 (95%)	0
Systolic pressure gradient	–	38/38 (100%)
Murmur	2 (3%)	47/61 (77%)
Systolic hypertension	0	22/38 (58%)

TABLE 4. *Comparison between the clinical findings in our study and Ing study.*[11]

	Our study (%)	Ing study[11] (%)
Femoral pulse	39/44 (89)	43/50 (92)
Murmur	47/61 (77)	50/50 (100)
Hypertension*	22/38 (58)	47/50 (97)
SPG≥10 mm Hg	38/38 (100)	50/50 (100)
SPG≥20 mm Hg	32/38 (84)	47/50 (94)

*Systolic hypertension considered if systolic BP>95th centile (standard centile chart);[21] SPG=standard pressure gradient.

TABLE 5. *Systolic pressure gradient between upper and lower limbs (in patients with correct BP readings, 38/61).*

	Group A	Group B	P-value
Number	15	23	
Mean	69.1	39.1	0.02*
SD	45.7	31.2	
Mode	110	30	
Median	44	32	
Minimum	20	10	

*Significant.

The cardinal features of coarctation of the aorta vary in their sensitivity. 1) Femoral pulse: palpation of femoral pulse is a reliable method of screening for coarctation in children.[11] This was abnormal in 89% of our patients and 92% in a study by Ing et al.[11] 2) Murmur: although 100% of patients in the Ing study had a murmur, only 77% of our patients had murmur. 3) Systolic hypertension was found in 47/51 patients (94%) in the Ing study, but only in 22/38 patients (58%) in our study. Differences in incidence of murmur and systolic hypertension between our study and the Ing study could be explained by patients' age (all of our patients were below the age of one year, but all the patients of Ing were over the age of one year). 4) Systolic pressure gradient: all of our patients, as well those of Ing, had SPG ≥10 mm Hg, but 32/38 of our patients (84%) and 47/50 of Ing's patients (94%) had SPG ≥20 mm Hg. A comparison between clinical findings in our study and those of Ing is presented in Table 4. It seems that the most reliable clinical sign for detection of coarctation of the aorta is systolic blood pressure gradient between the arms and legs.

Blood pressure measurement is not difficult with the availability of automated oscillometric machines. Experience with an automated oscillometric blood pressure machine has been found to be highly accurate in recording both upper and lower extremity blood pressure in the newborn infant.[11,21]

Patients with COA associated with other cardiac lesions had significantly (P=0.02) lower mean SPG (39.1 mm Hg ±31.2) than patients with isolated COA (69.1 mm Hg ±45.7) (Table 5). So, SPG in the lower range of significance (SPG: ≥10 mm Hg) can be considered to be an indicator for complex cardiac lesions rather than isolated COA in symptomatic patients below the age of one year.

With regards to earlier presentation of patients with COA associated with other cardiac lesions, our finding is similar to other studies. Our patients with coarctation and associated cardiac lesions presented earlier than patients with isolated coarctation, but the difference was not statistically significant (P=0.72). This could be explained by the fact that we included only inpatients, excluding patients with mild or moderate degrees of isolated coarctation.

Efforts at increasing the awareness of primary health physicians about the importance of the neonatal screening examination and of measuring BP in all limbs to detect early COA is vital. Timing the neonatal screening examination between the third day and third week after delivery is recommended. Any child with hypertension should be specifically evaluated for COA. SPG between upper and lower limbs is a sensitive indicator for COA, and it is recommended to be used as a screening test.

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A LOGISTIC REGRESSION MODEL TO PREDICT NODAL MALIGNANCY AMONG CASES WITH LYMPHADENOPATHY

Gaafar M. Malik, MRCP; Mostafa A. Abolfotouh, MPH, DrPH; Suliman Jastania, FRCSEd;
Nader Morad, FCAP; Eldawi N. Eltayeb, FRCSI, FRCSEd; Gulam Saydain, MD

Background: Peripheral lymphadenopathy can be caused by benign and malignant diseases. In this logistic regression model, we attempted to identify the clinical findings predicting high probability of nodal malignancy.
Materials and Methods: Two hundred and twenty cases diagnosed by peripheral lymph node biopsy were studied. Of these, 164 had benign lymph node pathology, while the other 56 were malignant. The patients' medical charts were reviewed and a logistic regression model used to identify physical signs and simple investigations that will predict nodal malignancy.
Results: Hard lymph node consistency, negative Mantoux test and positive abdominal ultrasound (showing hepatosplenomegaly with or without lymphadenopathy) were found to correlate with a higher probability of nodal malignancy.
Conclusion: A logistic regression model is proposed to calculate the probability of lymph node malignancy at different ages and both sexes in relation to lymph node consistency, Mantoux test and abdominal ultrasound results.
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Key Words: Lymph node, Mantoux test, abdominal ultrasound, hard node.

Peripheral lymphadenopathy can be caused by benign and malignant diseases.[1] The most common benign causes include granulomatous lymphadenitis and reactive lymphoid hyperplasia, while the most common malignant causes include lymphoma and metastatic cancers.[2] Although lymph node biopsy is the final method to differentiate between benign and malignant nodes, several investigations are known to be helpful, including ultrasound and CT of nodes.[3,4] In this study, by reviewing the histopathological results of 220 lymph node biopsies and correlating the result with clinical findings and simple investigations, we attempted to develop a model predicting nodal malignancy from the age and sex of the patient, consistency of lymph node, result of Mantoux test and abdominal ultrasound.

Materials and Methods

Cases of lymphadenopathy seen in Asir Central Hospital, Abha, in Southwest Saudi Arabia during the period 1992-1995 inclusive, were studied retrospectively. A total of 220 cases in which lymph node biopsy was done with an available histopathological report were included in the study. Of the number, 113 were males, with a mean age±SD of 31.84±21.39 years (range 4 months to 100 years). One hundred and sixty-four patients were diagnosed as benign, with cases of caseating granuloma (72), reactive hyperplasia (71), noncaseating granuloma (5) and nonspecific lymphadenitis (16). The remaining 56 were malignant, including non-Hodgkin's lymphoma (19), Hodgkin's lymphoma (17) and metastatic carcinoma (20). The patients' charts were reviewed for demographic data, duration of lymphadenopathy, site of lymph nodes, their consistency, presence of hepatosplenomegaly, result of Mantoux test and abdomen ultrasound.

The Mantoux test was performed by injecting 5 tuberculin units of PPD intradermally, and the result measured after 72 hours. A result of 10 mm or more was considered positive. A positive abdominal ultrasound was the one showing hepatosplenomegaly with or without lymphadenopathy.

Data was analyzed using SPSS for Windows® statistical software. Chi-squared test was applied to compare categorical data, and Mann-Whitney test for comparison of quantitative data. Significance was assumed if P-value was less than 0.05.

From the Departments of Medicine (Dr. Malik), Family and Community Medicine (Dr. Abolfotouh), Surgery (Dr. Jastania), and Pathology (Dr. Morad), College of Medicine, King Saud University, and the Departments of Surgery (Dr. Eltayeb) and Medicine (Dr. Saydain), Asir Central Hospital, Abha, Saudi Arabia.

Address reprint requests and correspondence to Dr. Malik: Associate Professor of Medicine, College of Medicine, King Saud University, Abha Branch, P.O. Box 641, Abha, Saudi Arabia.

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Logistic regression model was applied using the Wald statistical technique to show the value of the above clinical findings and investigations in predicting nodal malignancy.

The logistic regression analysis is a statistical technique through which one can examine the relationship between a dependent variable and a set of independent variables, and select the independent variables which could provide the best prediction possible of the dependent variable and exclude the others with no association. The following variables were used in this model.

a) Dependent variables: y=histopathology of lymph node, coded as follows: 0=non-malignant, 1=malignant.

b) Independent variables, x as follows:

1. x_1 = dummy variable used for sex as follows:
   x_1, 0 =female.
   x_1, 1 =male.
2. x_2= dummy variable for age in years as follows:
   x_2, 0 = age 60 years or less.
   x_2, 1 = age more than 60 years.
3. x_3 = dummy variable for Mantoux test as follows:
   x_3, 0 = negative Mantoux.
   x_3, 1 = positive Mantoux.
4. x_4 = Dummy variable for nodal consistency as follows:
   x_4, 0 = not hard.
   x_4, 1 = hard
5. x_5= Dummy variable for ultrasound abdomen as follows:
   x_5, 0 = normal.
   x_5, 1 = abnormal.

The general form of the regression model is as follows:

$$z= \beta_0+ \beta_1 x_1+ \beta_2 x_2 \ldots\ldots + \beta_p x_p$$

where z = the linear combination, β_0 = constant.

$\beta_1, \beta_2, \ldots\ldots \beta_p$ are partial regression coefficients.

$x_1, x_2, \ldots\ldots x_p$ are the independent variables.

Results

Table 1 shows the univariate association of nodal malignancy with different demographic and clinical findings. It shows a significant association between nodal malignancy and each of the five variables, i.e., age (P<0.0001), sex (P=0.02), lymph node consistency (P=0.006), Mantoux test (P=0.02) and abdominal ultrasound result (P=0.007). The logistic regression analysis was applied with those five variables as independent variables against lymph node pathology as the dependent variable (Table 2). When the regression model was assessed for goodness of fit, 70.85% of all cases were found to be correctly classified according to the pathology of lymph nodes.

Table 2 contains the estimated coefficients and their exponential from the logistic regression model that predicts nodal malignancy from a constant and the variables, sex (1 for male), age in years, Mantoux test (1 for positive), lymph node consistency (1 for hard) and ultrasound abdomen (1 for abnormal ultrasound, showing hepatosplenomegaly with or without lymphadenopathy). The model chi-squared is 25.109 and is significant at the 0.0001 level, indicating that the probability of obtaining the result by chance is less than 1 in 10,000. Age was the best predictor of nodal malignancy. The association of malignancy and age was direct, meaning that the increase in age was associated with a greater likelihood of malignancy (P=0.004). Since the exponential (ß) for Mantoux is less than 1, Mantoux result is an inversely related factor for nodal malignancy. The other variables, including old age group, hard lymph node and abnormal ultrasound of abdomen, all favor nodal malignancy.

TABLE 1. *Association of nodal malignancy with some demographic and clinical findings.*

Variable	P-value
Age	<0.0001*
Sex	0.02*
Nationality	0.77
Duration of lymphadenopathy	0.16
Site of lymph nodes	>0.05
Nodal distribution (generalized or localized)	0.12
Lymph node consistency	0.006*
Hepatomegaly	0.51
Splenomegaly	0.23
Positive Mantoux test	0.02*
Abnormal abdominal ultrasound	0.007*

*Denotes significant association at 0.05 level of significance.

TABLE 2. *Variables that predict nodal malignancy and their coefficients and exponentials using logistic regression model.*

Variable	Coefficient (β)	SE	P-value	Odds Ratio
Sex (1=male)	0.877	0.453	0.05	2.403
Mantoux (1=+ve)	-1.553	0.826	0.06	0.212
Node consistency (1=hard)	0.846	0.487	0.08	2.330
Ultrasound abdomen (1=abn.)*	0.756	0.485	0.12	2.130
Age in years	0.028	0.010	0.004	1.029
Constant	-2.304	0.560	0.0001	

SE=standard error; *abnormal abdominal ultrasound showing hepatosplenomegaly with or without lymphadenopathy.

Given the previous coefficients, the logistic regression equation for the probability of nodal malignancy can be written as follows:

Probability of nodal malignancy = $1/\,\underline{1 + e^{-z}}$,where e stands for exponential.

z=–2.304 + 0.877 (sex) + 0.028 (age) + 0.846 (node consistency) – 1.553 (Mantoux) + 0.756 (US abdomen result).

Applying this to a male patient who is 60 years with the values of zero for the remaining independent variables, we find:

$$z=-2.304 + 0.877\ (1) + 0.028\ (60)=0.253.$$

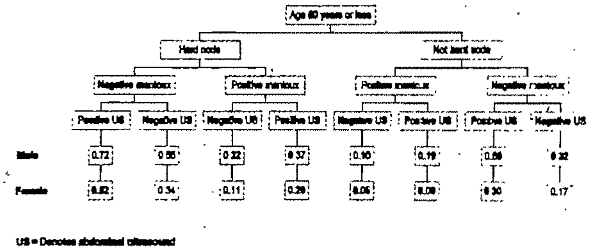

FIGURE 1. Predicting nodal malignancy in patients aged 60 years or less.

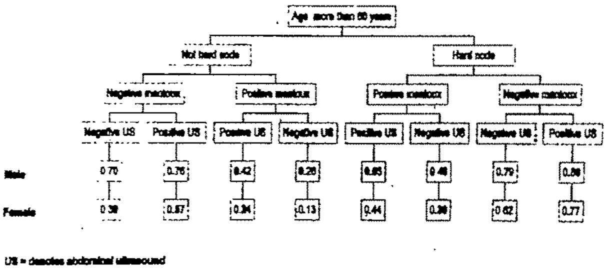

FIGURE 2. Predicting nodal malignancy in patients over 60 years or age.

The probability of nodal malignancy is then estimated to be :

Probability $=1/1 + e^{-z} = 1/1 + e^{-(0.253)} = 0.57$.

Based on these (sex and age alone), we would predict that nodes are 0.57 likely to be malignant. Following the same procedure as before for a male patient 60 years old and adding a value of 1 for lymph node consistency (hard), the estimated probability of malignant node is: $1/1 + e^{-(1.1223)} = 0.75$, that is to say, the nodes are more likely to be malignant. However, in the same patient, if the Mantoux is positive (value of 1) and the abdominal ultrasound is negative (value of zero), the probability will drop to 0.39. If the ultrasound is positive (value of 1), the probability will rise to 0.58, indicating higher possibility of malignant nodes.

Figure 1 shows the probabilities for both sexes aged 60 years or less at different combinations of lymph node consistency, result of Mantoux and abdominal ultrasound, while Figure 2 predicts the probabilities for both sexes above 60 years of age, based on the following regression model:

$$z = -1.5930 + 0.8541\,(\text{sex}) + 1.11446\,(\text{age group}) + 0.9436\,(\text{nodal consistency}) - 1.4442\,(\text{Mantoux}) + 0.7280\,(\text{abdominal US}).$$

Thus a working plan derived from Figures 1 and 2 could be cited as follows:

For patients 60 years of age or less:

1. If lymph node is not hard, malignancy is unlikely.
2. If lymph node is hard, Mantoux is negative and abdominal ultrasound is abnormal, malignancy is likely, especially in males.
3. If lymph node is hard and Mantoux test is positive, malignancy is unlikely.

For patients who are more than 60 years of age:

1. If lymph node is not hard and Mantoux is negative, malignancy is likely, irrespective of abdominal ultrasound in males, but a positive ultrasound is needed to increase probability in females.
2. If lymph node is not hard and Mantoux is positive, malignancy is unlikely, irrespective of abdominal ultrasound result in both sexes.
3. If lymph node is hard and Mantoux is negative malignancy is likely, irrespective of abdominal ultrasound in both sexes.

Discussion

Our model shows that if the lymph nodes are not hard in patients under 60 years of age, the probability of malignancy is low. If the lymph nodes are not hard and the Mantoux is positive and abdominal ultrasound is normal, the probability becomes very low, i.e., 0.05 for females and 0.10 for males (Figure 1). However, if the Mantoux is negative and the abdominal ultrasound is positive, the probability will increase to 0.50 for males and 0.30 for females. If the node is hard and the Mantoux is positive, the probability will be 0.37 for males and 0.20 for females. However, if the Mantoux is negative and the abdominal ultrasound is positive, the probability will increase to 0.72 for males and 0.52 for females. Previous studies using simple clinical criteria to differentiate between benign and malignant nodes gave different results. One has shown low predictive values of clinical criteria.[5] Another study using clinical criteria to decide which node will need biopsy in children gave high predictive values up to 97%.[6] From our study, it seems that if a lymph node has a hard consistency, then a negative Mantoux test and a positive abdominal ultrasound are more useful in predicting nodal malignancy. Negative Mantoux test has been shown to be associated with malignant conditions such as lymphomas,[7] cervical cancers with lymphadenopathy,[8] metastatic breast cancer[9] and colon and stomach cancer.[10] In causes of benign lymphadenopathy, like tuberculosis, studies have shown a very high positive rate of Mantoux in children and adults.[11,12] One study from Ethiopia found that the Mantoux result is helpful in predicting nodal malignancy.[13] Abdominal ultrasound in malignant diseases was found to be helpful in showing abdominal nodal spread.[14]

In patients over 60 years of age, our model shows that a negative Mantoux and positive abdominal ultrasound have a predictive value of 0.76 for males and 0.57 for females if the lymph node is not hard (Figure 2). However, if the node is hard, the negative Mantoux and positive abdominal ultrasound will increase the probability of nodal malignancy to 0.89 in males and 0.77 in female. The increased probability of malignancy with hard nodes in elderly patients can be explained by the fact that malignancy increases with age, and the chance for a hard node to be malignant is higher in elderly than in young patients. The higher rate of malignancy in patients above 60 years of age can also be explained by the fact that cellular immunity decreases with age, and this has been shown to be associated with higher rates of malignant disease.[15]

This logistic regression model could be helpful in identifying patients with low probability of malignant nodes who can be spared lymph node biopsy if their clinical features are not suggestive of a treatable cause such as tuberculosis or malignancy. When assessing the validity of such a clinical prediction of nodal malignancy, it was found that a specificity of 74% was detected at a cut-off value of probability of 0.40, a finding that results in 26% of cases doing an unnecessary biopsy, based on these clinical criteria. On the other hand, the negative predictive value of such a cut-off point is 78%, denoting that 22% of those classified as non-malignant on clinical settings are in fact malignant, and will benefit from nodal biopsy. However, further prospective studies, including larger number of cases, are needed to confirm the validity of this type of clinical prediction.

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PREVALENCE OF HEADACHE AND MIGRAINE IN SCHOOLCHILDREN IN THE UNITED ARAB EMIRATES

A. Bener, MD; H. Swadi, MD; E.M.A. Qassimi, MD; S. Uduman, MD

Background: The aim of this report was to study the prevalence of headache and migraine among schoolchildren in the United Arab Emirates, and to determine the relationship between headache and various factors, with special emphasis on migraine, and the impact of headache on school attendance.

Materials and Methods: A cross-section population study was performed over a period between October 1995 and June 1996. Subjects were selected by multistage stratified sampling procedure. Data was collected by screening questionnaires followed by clinical interviews. This involved children of 12 primary schools in Al-Ain, Dubai, and Sharjah Emirates, for a total of 1159 schoolchildren.

Results: The prevalence rate of headache was estimated to be 36.9%, and for migraine 3.8%. The study showed that the prevalence of headache increases with age, the highest rate being among 13-year-olds (17.5%).

Conclusion: The prevalence rate of headache and migraine in our study was similar to that found in other parts of the world. However, cultural and social factors may play a role in determining the incidence rate in this region.

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Key Words: Headache, migraine.

Headache is a common symptom and complaint in pediatric practice,[1-3] but consultation rates do not reveal the true prevalence.[4] Moroever, much less is known about the prevalence and causes of headache in non-hospital populations among schoolchildren.[5] Migraine is said to be the most common cause of primary headache in children.[6-8] The classic work of Bille on childhood headache and migraine in Sweden provided the first well-conducted population-based study.[6] The diagnostic criteria for migraine, defined by the International Headache Society[9,10] are now widely accepted and have been applied successfully to studies on the epidemiology of migraine in adults.[11,12]

Epidemiological studies in migraine have reported the role of genetic[13,14] and sociodemographic factors,[15] and several lines of evidence suggest that race may also be an important determinant of the prevalence of migraine.[16] The present study aims to determine the prevalence rate of headache and migraine in a random sample of schoolchildren aged 6-14 years in the United Arab Emirates, as defined by the International Headache Society criteria and validation of the questionnaire responses with clinical interviews.

Materials and Methods

Study Design

This was a cross-sectional population-based study conducted in Al Ain, Dubai, and Sharjah Emirates in the United Arab Emirates (UAE). The survey was performed to study the association between headache and migraine, and sociodemographic, genetic and environmental factors deemed to be the most important determinants. The survey was conducted among UAE national children aged 6-14 years. The diagnostic criteria for migraine were those defined by the International Headache Society.

Data Collection

A representative sample of 1400 UAE national schoolchildren aged 6-14 years were included in this study, which was conducted between October 1995 and June 1996. All information was based on structured prospective personal interviews in Arabic, by physicians and qualified nurses.

A multi-stage stratified cluster sampling design was developed using the administrative division of the UAE into three Emirates of approximately equal size in terms of number of inhabitants. In order to secure a representative sample of the study population, the sampling plan was stratified with proportional allocation according to stratum size.[17] According to the 1995 Ministry of Health Annual Report, the total population was 2.3 million. UAE nationals constitute 30% of the total population. Stratification was based upon geographical location. The

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From the Departments of Community Medicine, Psychiatry, Family Medicine and Pediatrics, Faculty of Medicine and Health Sciences, UAE University, Al-Ain, United Arab Emirates.

Address reprint requests and correspondence to Dr. Swadi: Department of Psychiatry, Faculty of Medicine and Health Sciences, UAE University, P.O. Box 17666, Al-Ain, United Arab Emirates.

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sample size was determined with the a priori knowledge that the prevalence rate of migraine and headache in the UAE is more or less similar to Western countries; or that it may be affected by parity, heredity, climate and sociodemographic and environmental factors. Allowing an error of 2.5% and level of significance (Type-I error) of 1%, it was believed that a sample size of 1400 was adequate to achieve a high degree of precision in estimating the true prevalence rate of migraine and headache in the general population. Therefore, on computing for 99% confidence limits and with 2.5% error bound, it yielded the required sample size of 1400. This was considered the target population. The subjects selected from each region were predetermined to be proportional to the size of Emirates and Medical Health Districts. Furthermore, schools and classes were then selected proportionally and randomly. Within the randomly selected classes, a quota of randomly selected students completed the survey.

Statistical Method and Analysis

The questionnaires were coded, entered and processed in the Department of Community Medicine on the IBM computer of the Faculty of Medicine and Health Sciences at the United Arab Emirates University. The statistical package program SPSS[18] was used to calculate chi-square, to ascertain the association between two or more categorical variables. In 2x2 tables, the Fisher's exact test (two-tailed) was used instead of the chi-squared test, especially when the sample size was small. Student's *t*-test (two-tailed) was used to determine the significance of difference between two continuous variables. The level $P<0.05$ was considered as the cut-off value for significance.

Results

The original sample included approximately 1400 students, but the total number for analysis was 1159, due to losses from school absence and incomplete questionnaires, resulting in a response rate of 82.7%. Of the total population, 428 (36.9%) reported recurrent headache over the previous year. Furthermore, 190 (16.4%) reported recurrent headache which was severe enough to stop or interfere with normal daily activities. Those who reported recurrent headache missed a mean of 3.5 (SD 4.3) days of school in the previous term because of headache. Those who did not report headache missed, on average, 2.7 (SD 3.1) days of school during the same period (*t*-value 3.10, P=0.002). Only 221 of the parents (19.1%) could report a cause for the headache. The prevalence of recurrent complaints of headache ranged from 9% to 11% until the age of 13 years, when it peaked at 17.5%. There were no significant differences between the three cities in terms of prevalence of headache and of migraine, as shown in Table 1.

We examined some variables which we thought would be of interest to the health of the community. We were interested in home environment, school environment, and role models for headache. We compared children who reported headache with those who did not. Cross-tabulation of the results is shown in Table 2. Only small variations in the number of respondents to those items in the questionnaire occurred.

The next question was how many children suffered from migraine. We used the International Headache Society criteria[9] to define migraine. Using these criteria, 44 (3.8%) were classified as having migraine. However, 378 (32.6%) reported the attacks as lasting more than two hours in most instances, but not fulfilling enough of the research criteria for migraine. Of the children who had migraine, 20 (45.5%) had migraine without aura, 13 (29.5%) had migraine with aura, and 18 (40.9%) had ophthalmoplegic migraine. In those children who were reported to have migraine, 14 (31.8%) reported general undefined family problems, 14 (31.8%) had school problems and 29 (65.9%) gave a history of recurrent headaches in a parent. These were significantly different from rates reported in children without headache.

Discussion

There are no data on headache and migraine among UAE children because no studies have been conducted in this area. The small sample size and the use of only questionnaires as a way of collecting the data restrict the generalization of the results. However, some observations on the prevalence of headache can be determined by this study. Prevalence studies of migraine among schoolchildren have been reported in different countries, such as Finland,[8] Denmark,[11-13] USA,[15,16] Australia,[19] Great Britain,[3,5,20] and Sweden.[6,21] These reports suggest that the prevalence rate varies between 3% and 10%,

TABLE 1. *Prevalence of headache and migraine in three cities in the UAE.*

City	Headache %	Migraine %
Al-Ain	37.8	3.6
Dubai	38.4	4.1
Sharjah	34.5	3.7

TABLE 2. *Comparison variables between children with headache and those without headache.*

Variable	Children with headache	Children without headache	*P*-value
	N=428	N=731	
Family problems	78 (18.2%)	78 (10.7%)	0.0003
School problems	97 (22.7%)	103 (14.1%)	0.0002
Parent(s) often complaining of headaches	196 (46.2%)	479 (68.9%)	0.0001

depending on the age range investigated and the method of investigation. The rates of recurrent headache are considerably higher, ranging between 20% and 50%.[21-24]

Our findings show a similar pattern to that reported elsewhere. However, our culture is different and the explanations for these prevalence rates may vary. Somatization is common in the Middle East, and parents (particularly women) often complain of headache as a representation of psychological symptoms. Children are likely to use their parents as role models, as shown by our findings.

Another possible explanation is the genetic loading factor, particularly for migraine. Our results are consistent with others which suggest that family conflict, emotional factors and educational pressures are important in determining the prevalence of headaches.[25-27] It was interesting to note that the prevalence of headache among children living only with their mothers was 64.7%, compared to 57% in those living with intact families.

Our data showed that the highest prevalence rate of headache occurred among those aged 13 years, indicating that the prevalence increases at puberty, as has been found in other studies.[2] The increase of the prevalence rate in 13 year olds and above, particularly girls, is also in agreement with other studies.[8,21,22] This may be related to biological factors (usually hormonal) at this stage of development. However, there are other possibilities that may be culturally determined. In this culture, academic achievement by children is an extremely pertinent issue. Often the emphasis is on achieving high grades in examinations at the expense of enjoyable learning. Children are often subjected to these stresses, and complaints of headache are common, particularly during the examination season. The second cultural issue is the stress of social restrictions, particularly on teenage girls. Social expectations of girls are different from those of boys in relation to personal freedom, choices and peer relations. Often this can be a source of conflict, anxiety and mood problems—factors known to be associated with headache.[28]

In conclusion, the prevalence of headache and migraine among schoolchildren in this country are similar to other parts of the world, but there may be culturally set factors that play a role in determining the extent of these phenomena. Consanguineous marriages, social expectations, social restrictions and role models (particularly in relation to somatization), seem to be prime candidates. A more rigorously designed and narrowly focused investigation is currently being planned to investigate the influences of these variables.

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Review Article

DRUG-INDUCED RHABDOMYOLYSIS

E.B. Larbi, MB, PhD, FRCP

The syndrome of rhabdomyolysis is the result of skeletal muscle injury that alters the integrity of the sarcolemma and leads to the eventual release of intracellular contents into the plasma. The causes are diverse, and include muscle trauma (for instance, from vigorous exercise, crush injuries, battering, or seizures), inadequate blood perfusion, heat stroke, electrolyte imbalance, hereditary enzyme deficiencies, infections and ingestion of drugs and toxins. Various serious medical disorders, particularly those resulting in states of disordered energy production, are also associated with rhabdomyolysis.

In general, drug toxicity involves organs, such as the kidney, liver, gastrointestinal tract and the central nervous system, with skeletal muscle being usually less readily affected. Although drug-induced rhabdomyolysis was uncommon in the past, it is no longer rare, due to the introduction of more and increasingly potent drugs into clinical practice.

The incidence of drug-induced rhabdomyolysis is uncertain, largely because most of it is unreported. Similarly, the mortality rates are unknown. However, it has been suggested that rhabdomyolysis from all causes leads to 5%-25% of cases of acute renal failure.[1,2] Furthermore, about 10%-40% of patients with rhabdomyolysis develop acute renal failure.[3-5]

Rhabdomyolysis can result from direct muscle injury by myotoxic drugs, such as cocaine and alcohol. This mechanism must be distinguished from rhabdomyolysis that develops secondarily from muscle ischemia due to prolonged seizures or local muscle compression in comatose states following drug overdosage.

Mechanisms

A large number of drugs can cause rhabdomyolysis through various mechanisms, which are probably multifactorial (Table 1). Any drug which directly or indirectly impairs the production or use of adenosine triphosphate (ATP) by skeletal muscle, or increases energy requirements so as to exceed ATP production, can cause rhabdomyolysis.[6,7] The processes include ischemia as a result of prolonged immobilization from drug overdosage with CNS depressants, thus impairing the delivery of oxygen and nutrients, drug-induced delirium, choreoathetosis, dystonic reactions and seizures (which increase muscle activity and the demand for ATP). Drugs can also be directly toxic to muscle cells, interfering with the production or use of ATP.

The potential mechanisms of drug-induced sarcolemmal injury, as reviewed by Knochel[8] and Armstrong et al.,[9] are as follows. A change in the viscosity of sarcolemma is caused by activation of phospholipase A. It results in increased permeability of the sarcolemma, permitting leakage of intracellular contents, as well as an increase in the entry of sodium ions into the cell. The increased intracellular sodium ion concentration activates Na^+,K^+-ATPase, a process which requires energy. This eventually exhausts the supplies of ATP and thus impairs cellular transport.[10] The increase in cellular sodium ion concentration also leads to an accumulation of intracellular calcium ion concentration, which activates neutral proteases within the cell, causing further cellular injury.[9] However, it has been suggested that, irrespective of the mechanisms involved, there is a final common pathway,[8] namely, there is an increase in the intracellular concentration of sodium ion, which in turn leads to an increase in the concentration of intracellular calcium ion. This enhances the activity of the intracellular proteolytic enzymes, leading to further destruction of intracellular structures.

There is another mechanism peculiar to the 3-hydroxy-3-methyl glutaryl coenzyme A (HMG-Co A) reductase inhibitors, which inhibit cholesterol synthesis. They reduce serum levels of coenzyme Q, a component of the electron transport chain. This affects oxidative phosphorylation.[11] The HMG-Co A reductase inhibitors inhibit the synthesis of mevalonate, the reduced supplies of which inhibit the formation of coenzyme Q.

Severe hypokalemia, especially that associated with significant reduction in intracellular muscle potassium content, has also been implicated in the pathogenesis of rhabdomyolysis. Glycogen synthesis is impaired in hypokalemic states, leading to a reduction in energy production during sustained muscle contraction.[12] Hypokalemia has been shown experimentally to reduce muscle cell transmembrane voltage and to cause muscle damage.[13] Contraction of muscle leads to the release of

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From the Departments of Internal Medicine and Pharmacology, King Faisal University, College of Medicine, Dammam, Saudi Arabia.

Address reprint requests and correspondence to Dr. Larbi: Departments of Medicine and Pharmacology, King Faisal University, College of Medicine, P.O. Box 2114, Dammam, Saudi Arabia.

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potassium ions into intracellular space. Concentrations as high as 15 mEq/L can be attained.[8] This has a vasodilator effect, which thus enhances the increase in muscle blood flow during exercise. In hypokalemic states there is no release of potassium from the contracting muscles, and so blood flow is not increased. Continued muscle contraction, therefore, leads to ischemia and muscle necrosis.[14]

Alcohol directly injures the sarcolemma and increases sodium permeability. This in turn increases the activity of the Na^+,K^+-ATPase pump, with the eventual exhaustion of energy stores. Increased cytosolic Na^+ enhances the accumulation of cytosolic Ca^{++}, which in addition to increased mitochondrial Ca^{++} causes cellular injury. Analysis of skeletal muscle from chronic alcoholics and experimental animals fed ethanol shows a marked depletion of potassium, phosphorus, and magnesium, and elevated sodium, chloride, calcium and water content.[15,16] Acute hypophosphatemia would shut off ATP synthesis. Uniform muscle necrosis, leukocyte and macrophage invasion of degenerated muscle fibers are observed with light microscopy, and ultrastructural changes include the separation of myofibrils and other cellular elements by clear spaces.[17,18]

Acute alcohol-induced rhabdomyolysis can occur after binge drinking or a sustained period of alcohol abuse, and is associated with pain and swelling of muscles, particularly the quadriceps.[17] Symptoms resolve if the patient abstains from alcohol use.[19]

Serious drug poisoning is frequently associated with rhabdomyolysis, although the incidence is uncertain. The mechanisms involved vary with the drug. General anesthetic agents and overdosage with central nervous system drugs, such as narcotics, cyclic antidepressants, benzodiazepines, antihistamines and barbiturates, cause rhabdomyolysis by pressure-induced ischemia due to prolonged immobilization.[20-24] Drugs such as LSD, sympathomimetics and phencyclidine,[5] which induce delirium or agitation, and those which cause prolonged involuntary muscle contraction (e.g., phenothiazines and butyrophenones), lead to increased ATP demand and eventual exhaustion of its stores.

Hyperthermia also increases the energy requirements of muscle and contributes to its damage. Cocaine and salicylate intoxication-induced rhabdomyolysis is due partly to the associated hyperthermia.[25] Cocaine, in addition, produces a syndrome similar to neuroleptic malignant syndrome associated with intermittent dystonia, alternating with substantial agitation, thus further increasing the ATP requirement.[26] Halothane-induced rhabdomyolysis results from the production of malignant hyperthermia (in predisposed patients) and a resultant increase in ATP requirement.

The frequent causative agents include psychotropic and central nervous system depressant drugs, as well as alcohol. The occurrence of rhabdomyolysis is further enhanced in the presence of predisposing factors, namely, hypokalemia, hyponatremia, hypernatremia, magnesium and phosphorus depletion, hypothermia or hyperthermia, diabetic ketoacidosis or hypertonic states.

TABLE 1. *Drugs which can cause rhabdomyolisis.*

Antipsychotics and antidepressants	
Amitriptyline[24]	Phenelzine[58]
Amoxapine	Perphenazine[24]
Doxepine[52]	Promethazine[59]
Fluoxetine[53]	Chlorpromazine
Fluphenazine[54]	Loxapine[60]
Haloperidol[55]	Promazine[59]
Lithium[56]	Trifluoperazine
Protriptyline[57]	
Sedative hypnotics	
Benzodiazepines:[22]	-Lorazepam[22,24]
-Diazepam[66]	-Triazolam[66]
-Nitrazepam[71]	Barbiturates[21]
-Flunitrazepam[75]	Gluthetimide[21]
Antilipemic agents	
Lovastatin[65]	Clozafibrate[69]
Pravastatin[11]	Ciprofibrate[70]
Simvastatin	Clofibrate[64]
Bezafibrate[68]	
Drugs of addiction	
Heroin [34,61]	Amphetamine[63]
Cocaine[25,26,62]	Methadone[84]
Antihistamines[36]	
Diphenhydramine[66]	
Doxylamine[67]	
Others	
Alcohol[17,19,72-74]	Pentamidine[86]
Amphotericin B[87]	Phencyclidine[5]
Azathioprine[89]	Phenytoin[77]
Butyrophenones[55]	Phenylpropanolamine[78]
Emetics	Quinidine[76]
Epsilon-aminocaproic acid[33]	Salicylates[25]
Halothane	Strychnine[79]
Laxatives	Succinylcholine[82]
Moxalactam[85]	Theophyline[80]
Narcotics[20,21]	Terbutaline
Oxprenolol[88]	Thiazides[81]
Paracetamol[25]	Vasopressin[90]
Penicillamine	

Biochemical Features and Basis for Diagnosis

Injury to the sarcolemma and skeletal muscle cell results in the release of myoglobin, creatinine phosphokinase (CK), as well as other protein and nonprotein cellular contents into plasma. Among others, there occurs an increase of serum myoglobin, CK, aldolase, lactic dehydrogenase, potassium, phosphates, purines, uric acid, aspartate aminotransferase (AST), carbonic anhydrase III, as well as myosin heavy-chain fragments.

Estimation of myoglobin in the serum and urine is useful for the diagnosis of rhabdomyolysis, particularly in the early phases of the disease. Myoglobin is filtered by the kidney and appears in the urine when the plasma concentration exceeds 1.5 mg/dL.[27] It imparts a dark red brown color to urine when urine concentration exceeds 100 mg/dL. Myoglobin has a short half-life (2-3 hours), and is rapidly cleared by both renal excretion and metabolism to bilirubin.[4,28] Serum myoglobin levels, therefore, return to normal in about 6-8 hours, following cessation of muscle injury. Owing to its rapid clearance from plasma, its absence does not exclude the diagnosis of rhabdomyolysis.

Elevated creatinine phosphokinase is the hallmark of rhabdomyolysis. It rises within 12 hours of the onset of muscle injury, peaks in 1-3 days, and declines 3-5 days after cessation of muscle injury.[27] The half-life of CK is 1.5 days and so it remains elevated longer than serum myoglobin levels.

Hyperkalemia increases the risk of cardiac dysrrhythmia. The release of organic and inorganic phosphates from the injured muscles causes an increase in serum phosphate levels, which may elevate calcium phosphate product resulting in deposition of calcium salts in muscle and other tissues.[29] Hypocalcemia then ensues. However, in late stages of the disease, mobilization of calcium from damaged muscle results in hypercalcemia.[30] The released purine precursors are converted to uric acid, thus increasing its levels.

Carbonic anhydrase III is present in skeletal muscles but not in myocardium. An increase in its levels is thus more specific for skeletal muscle injury than CK.[31] Increase in myosin heavy-chain fragments is also more specific in skeletal than myocardial muscle injury.[32] The levels increase in about 4 to 7 days after muscle injury, and remain so even until after day 12.[32] Measurement of myosin heavy-chain fragments is particularly useful for the late diagnosis of rhabdomyolysis. Unfortunately, these tests are not readily available. Other biochemical abnormalities include increased serum levels of creatinine, hydroxybutyrate and lactic acid, thrombocytopenia, increased fibrinogen degradation products, prolonged prothrombin time and proteinuria.

Clinical Manifestations

There is wide variation in the clinical presentation of rhabdomyolysis. The classical triad of symptoms are muscle pain, weakness and dark urine.[4,6,29,33-35] The muscles can be tender and swollen, and there can be skin changes indicating pressure necrosis. However, these classical features are seen in less than 10% of patients.[4] Over 50% of patients may not complain of muscle pain or weakness.[4] Diagnosis becomes even more difficult in patients with altered mental state or levels of consciousness, who are unable to give a coherent history. Features related to the effects of drug poisoning can also predominate and the possibility of rhabdomyolysis can be missed. A high index of suspicion of rhabdomyolysis is thus necessary for early diagnosis.

Rhabdomyolysis should be suspected in patients presenting with drug poisoning, altered levels of consciousness, severe fluid and electrolyte abnormality, hyperthermia, hypotension, hypoxia, and states of increased muscular activity, such as seizures, agitation, strenuous muscle exercise or dystonia, particularly in patients with alcohol or substance abuse. Patients who have ingested neuroleptic drugs can present initially with dystonia, hyperthermia, or neuroleptic malignant syndrome characterized by fever, muscle rigidity, autonomic dysfunction and altered consciousness.

Acute Renal Failure

Acute renal failure, oliguric or nonoliguric, is the most common complication of rhabdomyolysis. It occurs in 10%-40% of patients.[3-5] Rhabdomyolysis also accounts for 5%-25% of all cases of acute renal failure.[1,2,36] The causes of the renal injury include direct nephrotoxicity of ferrihemate produced by the dissociation of myoglobin at pH 5.6 or less,[37] tubular obstruction due to protein, uric acid crystals and precipitates of myoglobin (myoglobin casts), and reduction in renal blood flow as a result of renal vasoconstriction.[38-40]

Intracellular iron is an important mediator of tissue damage.[41] As a transition metal it can donate and accept electrons, and its toxicity is due to its ability to catalyze oxygen- and non-oxygen-based free radical reactions. In rhabdomyolysis, the cytotoxic iron moiety is derived from heme, a product of myoglobin metabolism. In the renal tubules the iron so derived catalyzes free radical reactions, which are associated with lipid peroxidation.[42] The major mechanism of renal tubular damage in rhabdomyolysis is the mitochondrial free radical production which induces lipid peroxidation.[43] Procedures which chelate iron, or prevent or reduce the release of free iron, have been shown to have a protective effect, thus demonstrating the important role of iron in tubular damage in rhabdomyolysis.[42-44]

Acute renal failure is associated in the early phases with a marked rise in uric acid and hypocalcemia. The raised uric acid is due to rapid metabolism of muscle purines. Binding of calcium by damaged muscle and decreased levels of serum 1,25 dihydroxycholecalciferol[45] account for the observed hypocalcemia. The combination of hypocalcemia and hyperkalemia can result in ventricular dysrrhythmia and possible cardiac arrest. Acute renal failure is also associated with a disproportionate increase in serum creatinine levels as a result of the release of preformed creatinine from the damaged muscle into plasma. Currently there is no reliable factor of predictive value in those likely to develop acute renal failure. Involvement of myocardium and intercostal muscles and diaphragm can lead to acute cardiomyopathy and acute respiratory failure.

Compartment syndrome is not unusual in drug-induced rhabdomyolysis. The compartments containing anterior tibial, peroneal, lateral thigh, soleus, gluteal, deltoid and forearm muscles may be affected.[21,22,25] There is increased swelling and tenderness of the involved muscle, and the increased pressure in the compartment can be associated with decreased pulse and neuropathy in the affected limb. Re-elevation of CK levels can herald the onset of compartment syndrome. Immediate fasciotomy is required if intracompartment pressure exceeds 30-50 mm Hg,[23] in order to prevent the sequelae of limb contracture, ischemia and possible amputation.[36,46,47]

Management

The treatment of rhabdomyolysis consists of: 1) general measures; 2) attempts to prevent acute renal failure; 3) hemodialysis; and 4) other measures.

General Measures

General management of drug overdosage includes termination of further exposure, reduction of absorption, enhancement of metabolism and excretion of the offending drug as appropriate. Features of drug overdosage, particularly in comatose patients, namely, hypothermia, hyperthermia, hypoxia, hypovolemia and hypotension, should be identified and treated. Measures should also be taken to stop further muscle damage. These include control of excessive muscle activity, such as in severe agitation and convulsions and abnormal posturing in unconscious patients. Sedatives, or in some cases anticonvulsants, may be required to control convulsions. Overdosage with phenothiazines may require the administration of anticholinergic agents to control dystonic reactions.

Attempts To Prevent Acute Renal Failure

Early correction of hypovolemia reduces the incidence of renal failure.[30] Various types of fluid composition and infusion regimes have been suggested.[30,48] Other additional measures include continued infusion of 0.9% saline and the administration of mannitol following correction of hypovolemia in order to induce diuresis. Although it may be difficult, it is essential to maintain a urine output of 300 cc/hour or more.[30] Alkalinization of urine prevents the dissociation of myoglobulin into globin and ferrihemate, which are toxic to the renal tubules. The possibility of aggravation of hypocalcemia by large doses of bicarbonate should be borne in mind, although this is rather uncommon, especially if hypovolemia is corrected.[30,23] The administration of mannitol also reduces intracompartment pressure and its attendant complications.

Hemodialysis

The indications for hemodialysis are standard and include failure of conservative measures in the management of acute tubular necrosis, severe acidosis, rapid increase in serum potassium levels, and hypocalcemia.

Other Measures

Supplement of calcium in hypocalcemia is rarely required. Its administration may not only enhance the deposition of calcium in damaged muscles and lead to further muscle damage, but may also increase the level of hypercalcemia during the recovery phase.[1,49] Hyperkalemia may require treatment with sodium bicarbonate (usually 50-100 mmol), glucose (50 mL of 50% dextrose) and insulin (10 units regular), resin preparation, such as sodium polystyrene sulphonate (25-50 g resin mixed with 100 mL of 20% sorbitol given orally, or 50 g of resin and 50 mL of 70% sorbitol, mixed in 150 mL of tap water, given as a retention enema), or as indicated above by dialysis.

Prognosis

The prognosis depends on the underlying drug toxicity, which may contribute to the reported mortality of about 5% observed in serious rhabdomyolysis.[4,5,36,50] Most cases are, however, mild. If there are no other underlying complications, acute renal failure in rhabdomyolysis is reversible and has an excellent prognosis, although recovery may be delayed. Early recognition and treatment of compartment syndrome prevents permanent disability.

Most cases of drug intoxication may be associated with rhabdomyolysis. It is thus fairly common. In a majority of cases, however, symptoms may be absent or mild. Its recognition and diagnosis, therefore, depend on a high index of clinical suspicion. The prognosis depends on the other effects of the offending drug, complications and severity of rhabdomyolysis. However, with appropriate treatment, the outcome is generally good.

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Special Communication

SURGICAL MANAGEMENT OF BREAST CANCER IN SAUDI ARABIA: A CALL FOR IMPROVEMENT

Bilal Al Jiffry, MBBS; Adnan Ezzat, FRCP; Jan Hildell, MD, PhD; H. Kfoury, MD, FRCPA;
Assem Rostom, FRCR; Olle Sjoklint, MD; Saif S. Al Sobhi, FRCS, ABIS;
Ralph Sorbris, MD, PhD; Robert Stuart, MD; Stig Ingemansson, MD, PhD

In carefully studied populations of the world, the incidence of breast cancer among women has shown an increase of 50% from 1960 to 1995. However, through screening programs and highly specialized, experienced multidisciplinary teams using all modern diagnostic and therapeutic modalities available, the mortality has decreased and the relative survival (at 2, 5 and 10 years) has increased in this period.

If age-specific incidence rates for Japan and USA were applied to the estimated female Saudi population in 1994, the yearly number of new breast cancer cases would be around either 500 or 3200. In 1994, 437 cases were reported in the country.[1]

At King Faisal Specialist Hospital and Research Centre (KFSH&RC), 1723 patients with breast cancer were treated between 1975 and 1991.[1] We currently receive 250-300 new cases every year. Every new patient is assessed by a team composed of a medical oncologist, a radiation oncologist and a surgeon. The assessment is based on referral notes from the outside hospitals, history, physical examination, review of outside pathology slides and x-ray films. The patient is then discussed in a conference (with a radiologist, pathologist, radiation oncologist, medical oncologist and breast surgeon). The plan for the patient's further work-up treatment and follow-up is decided upon and implemented. All follow-up visits are done in a combined clinic (medical oncologist, radiation oncologist, breast surgeon and, if needed, pathologist and radiologist).[2,3]

This study was part of a review of our current standards for work-up, treatment and follow-up of breast cancer patients. The aim of the study was: 1) to assess the standard management of breast cancer patients before referral to KFSH&RC; 2) to compare this management with accepted international standards of diagnosis, i.e., triple assessment (TA) (clinical examination, mammography and fine-needle aspiration); and 3) to discuss actions for improvement of the management of breast cancer patients, if found necessary.

Patients and Methods

The medical records of 100 consecutive patients referred to KFSH&RC during 1996 for breast cancer were pulled. Data was extracted from the charts during a two-week period. Ninety-two charts were available for review during that time. All data from the charts were transferred to a database for this study. The 92 patients were all women between 25 and 71 years of age (mean=45.3; SD=12.06) from all parts of the Kingdom.

Results

Clinical Information

The referral notes mentioned palpable tumor size in 69.6%, tumor relation to the skin in 57.6%, and its relation to the underlying structures in 46.7% of the patients. The status of the ipsilateral axilla was mentioned in 69.6% of the notes, and information about the size of the tumor, together with its relation to underlying structures and to the skin, was available in 41.3%. The status of the tumor and axilla was accurately described to allow a clinical TNM classification in only 35.9% of the patients.

Information About Pre-Referral Diagnostic Procedures

Mammography was reported performed in 29.4% of the patients and the majority of those investigations were of suboptimal quality. In only half of these investigations, however, were reports conveyed to KFSH&RC. FNA was carried out in 46.0% of the patients. We received the cytology report in 73.6% of these, but FNA slides accompanied only 14.5% of the patients who had FNA.

Proper triple diagnosis (tumor size, mammography and FNA) had been done in 12% of the patients. Mammography, FNA and accurate clinical TNM classification was done in 8.7% of the patients before referral.

From the Departments of Surgery, Oncology, Radiology and Pathology, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia.

Address reprint requests and correspondence to Dr. Sorbris: Department of Surgery, MBC-40, King Faisal Specialist Hospital and Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia.

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TABLE 1. *Sequential tasks in the diagnosis, staging and management of suspected breast cancer.*

Triple diagnosis	Work-up	Treatment plan	Preoperative	Operative treatment options	Post-operative
Breast cancer diagnosis established if: Positive clinical findings Positive mammogram Positive FNA	Minimal work-up Chest x-ray CBC, including liver and bone profiles Extended work-up Bone scan CT or US abdomen PET scan	Discuss the patient with a multidisciplinary team	Chemotherapy Hormonal manipulation Radiotherapy	Surgery or not If surgery: Breast conserving Mastectomy Axillary lymph node exploration Sentinel lymph node biopsy Complete axillary dissection Immediate or delayed breast reconstruction	Chemotherapy Hormonal manipulation Radiotherapy

Surgery Performed Before Referral to KFSH&RC

Surgery had been performed in 84% of the patients prior to their admission to KFSH&RC. The procedures were classified as biopsy (Bx) in 31.6%, excision in 17.1%, breast-conserving treatment (BCT) in 10.5%, and mastectomy in 40.8%. Axillary node dissection had been performed on 51.3% of the operated patients, and 41.7% of the axillary node dissection specimens contained less than eight lymph nodes. In all, 98 operations were performed on 78 patients in the referring hospitals.

Pre-Referral Pathology Reports

Tumor size was reported in 63.2% and status of the tumor margins in 54.5% of the specimens. In 29.3% of the outside pathology reports, both tumor size and the status of the margins were mentioned. Histology slides accompanied 83.6% of the operated patients, but from these slides tumor margins could be evaluated at KFSH&RC in only 6.1%.

When the referral documents arrive at KFSH&RC, the patient is normally given an appointment in the "Combined Breast Clinic" (radiation oncologist, medical oncologist and breast surgeon) on the following Saturday morning. Joint clinical assessment and review of the history are done, and review of outside x-ray films and pathology slides are arranged. Further work-up is done when necessary, and four days later the case is presented, discussed, and treatment planned in the Wednesday morning Breast Tumor Conference attended by a pathologist, radiologist, medical oncologist, radiation oncologist and breast surgeon (Table 1).

Additional surgery was performed in 36 (39.1%) patients. BCT was performed in 12 patients, BCT and axillary dissections in six patients, mastectomy in seven patients, and mastectomy and axillary dissection in 11 patients. Therefore, in the 92 patients, 134 operations were ultimately performed. Radiotherapy was given to 74 of the admitted patients (80.4%) and adjuvant chemotherapy to 60 (65.2%).

Discussion

Triple assessment or TA (physical examination, mammography and FNA), when positive, has a diagnostic accuracy of almost 100%,[4] and for this reason, open biopsy is hardly ever indicated. If FNA is inconclusive, a core needle biopsy can often solve the problem and open surgical biopsy should be avoided and used only on rare occasions. When TA is positive for malignancy, the work-up is completed with chest x-ray, bone profile and liver function tests (LFT). When the physical examination or the laboratory data indicate possible metastases in liver and bone, or if the case is clinically advanced (T_4 or N_2), ultrasound or CT scan of the abdomen, and/or bone scan with eventual bone x-ray, are done. The multidisciplinary breast cancer group (medical oncologist, radiation oncologist, radiologist, pathologist and surgeon) then decide on a recommended treatment and follow-up plan for the patient (Table 1).

International standards require that TA be used in nearly all patients with a suspicion of breast cancer.[5] In only 12% of our 92 patients had TA been properly done. Only 29.4% of the patients had preoperative mammography done, less than half had FNA done, and only 35.9% of documented clinical findings allowed a TNM classification. Again, all these investigations require good training and lots of experience. Concerning mammography, continuous quality control is mandatory, not only of image quality, but also of the interpretation by the radiologists.[6,7] Work overload, lack of adequate staff or facilities, can very well explain the lack of proper preoperative work-up.[8] The majority of our patients had their first surgery done before a decision was made by a multidisciplinary team, and it has to be emphasized that surgery is not always the first step in the treatment of breast cancer today (Table 1). Unnecessary biopsies and incomplete axillary dissections should be avoided in the future. Our 92 patients had 134 operations instead of only 92. Despite 98 operations on 78 patients before the referral to KFSH&RC, 36 patients had to have additional surgery done in our institution and 75% of these patients had residual disease. In about 70% of the patients, neither tumor size nor resection margins were mentioned in the records. From available outside slides, it was impossible for our pathologist to judge margins and tumor size. When breast specimens are sent to the pathology laboratory, proper action and reporting procedures have to be followed.

In the mastectomy specimen, the pathologist should specify the location of the carcinoma (i.e., outer upper quadrant), size, multicentricity, presence or absence of an intraductal component, with special reference to the type and percentage of ductal carcinoma in situ (DCIS). The report should also include reference to the presence and absence of lymphovascular invasion. The presence or absence of calcifications corresponding to mammographic findings are important to mention. The nipple and the skin involvement (i.e., presence or absence of Paget's disease), as well as the status of surgical margins, are other important prognostic factors and should be evaluated and documented. The appearance of the uninvolved breast tissue should be mentioned in the final report.

In the partially resected breast specimen, the parameters are almost the same, however, specific mention of the amount of necrosis present in the tumor,[9] as well as the status of the margins, are crucial. A surgical margin is considered free when the carcinoma is at one low-power field from the inked margin, and the margin is reported as close when it is at one high-power field of this margin. Grading of the breast carcinoma is an important parameter which has good correlation with prognosis. The Scarff Bloom Richardson (SBR) grading system[10,11] is used at KFSH&RC for infiltrating ductal carcinoma. The specific subtypes of breast carcinoma, namely mucinous, medullary and lobular, are not graded. Grading of ductal carcinoma in situ is still controversial. Some authors have suggested grading of ductal carcinoma in situ based on cytonuclear differentiation, as well as on architectural, while others rely exclusively on histologic patterns, such as solid, comedo, cribriform, etc. Evaluation of estrogen and progesterone receptors should be performed by immunoperoxidase technique or any other established method.

This study demonstrates suboptimal diagnostic assessment, surgery and pathology from referring hospitals. With solid, high-quality basic data, the experienced, specialized, multidisciplinary team can offer the patient an optimal line of treatment with tuned-in neoadjuvant therapy, radiotherapy, surgery and adjuvant therapy. Specialization decreases mortality[12,13] and increases survival.[5] Chemotherapy and radiotherapy have a well-documented impact on survival.[5,13-15] Saudi Arabia seems to have a low incidence of breast cancer, yielding about 500 new cases per year. Considering that KFSH&RC already receives 300 new cases annually, and the internationally accepted number of new cases to a breast cancer center should be minimally 100, one or two other centers in the Kingdom could be established.[5] When the diagnosis is established by TA and a proper metastatic evaluation is done, the patient should ideally be referred to a breast cancer center for decision on the best treatment plan.

As a tertiary care hospital, KFSH&RC provides continuing medical education for referring hospitals. As a result of this study we will concentrate our educational efforts on: 1) The diagnosis of breast cancer by TA; 2) the multidisciplinary approach to treatment planning; 3) the surgery of breast cancer; and 4) the pathology report.

By using TA to diagnose breast cancer, unnecessary diagnostic surgery is avoided. Surgery is not always the first treatment step, and so discussion with a multidisciplinary team is mandatory after diagnosis. Incomplete axillary lymph node dissections can be avoided if surgery is centralized to hospitals with a minimum of 100 cases per year. Incomplete pathology reports make further management of the patients suboptimal.

To reach the referring hospitals, we are currently working on the following strategies: 1) Extension of our outreach programs to additional hospitals; 2) preparation of a manual for the management of breast cancer in Saudi Arabia; and 3) interpretation of a nationwide medical telecommunications network.

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Case Reports

ATYPICAL SCABIES IN SYSTEMIC LUPUS ERYTHEMATOSUS

J. Fernando Val-Bernal, MD, PhD; M. Carmen González-Vela, MD; Sonsoles Yáñez, MD, PhD;
Concepción Mira, MD; V. Martínez-Taboada, MD, PhD; V. Rodriguez-Valverde, MD, PhD

Recent reports have increasingly linked scabies with congenital or acquired immunosuppression. It is important to be aware of this form of infestation, because its unusual clinical signs may be easily overlooked. Scabies can mimic several diseases, including cutaneous or systemic lupus erythematosus (SLE).[1] However, the infestation has rarely been reported in patients with SLE. The objective of this report is to describe a rare case of atypical (exaggerated) scabies in SLE that illustrates a pitfall in the recognition of the infestation, since such recognition took place belatedly. We hope that this case will draw attention to the possibility of scabies whenever a widespread erythematosquamous dermatosis develops in a case of SLE.

Case Report

A 39-year-old woman had SLE for about 17 years, which was manifested as malar eruption, oral ulcers, leukopenia and arthritis. She also had a history of several episodes of pleural effusion. The patient was being treated with prednisone (30 mg/day), enalapril maleate (10 mg/day), and chloroquine (250 mg/day).

In September 1995, she presented with nonpruritic erythematosquamous plaques, without alopecia or scars in the scalp. She was treated with topical application of betamethasone valerate. Two months later, she developed a generalized papulosquamous eruption (Figure 1). Physical examination revealed erythematous and erythematosquamous papules without itching, particularly affecting abdomen, arms, legs and buttocks. Routine laboratory findings, including creatinine level, were normal. Serum protein electrophoresis demonstrated a polyclonal increase in gammaglobulin, and IgA was 663 mg/dL (normal, 90-450). Cryoglobulins were trace-positive (IgG, IgA). ANA was positive at 1:1280, with a homogenous pattern. The serum levels of C3 and C4 were within the normal range. The rest of the immunologic studies were normal or negative. Although there was no clinical or serological activity of the disease, the lesions were presumed to be secondary cutaneous lupus erythematosus. Two punch biopsies were performed and scabies was diagnosed. Treatment with 1% lindane lotion in two courses resolved the cutaneous manifestations of the patient. She remained asymptomatic 24 months without relapse of her skin lesions.

Materials and Methods

The patient fulfilled the revised 1982 criteria for SLE of the American Rheumatism Association. The surgical specimens were fixed in 10% buffered formaldehyde solution, embedded in paraffin, and routinely processed. Consecutive 4 µm sections were stained with hematoxylin and eosin. Immunohistochemistry stains were performed by using the streptavidin-biotin-peroxidase method and a Techmate 500-220 automated immunostainer (Biotek, Santa Barbara, CA, USA). With the use of a pressure cooker, sections were boiled for a short time in sodium citrate buffer prior to the staining. Diaminobenzidine was used as chromogen. The following antibodies were utilized: CD3 (monoclonal, Dako, Glostrup, Denmark,

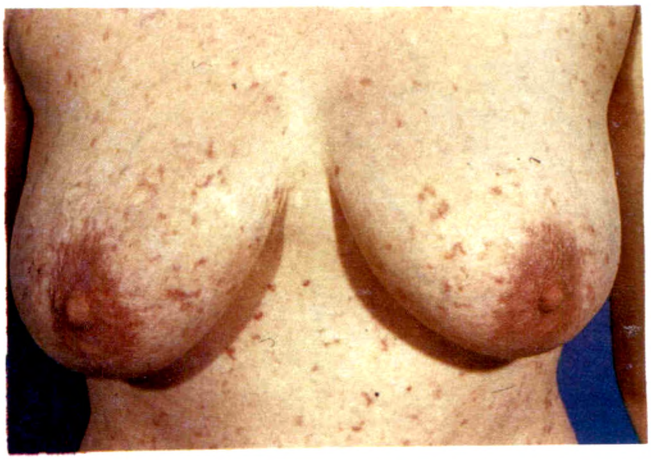

FIGURE 1. Clinical appearance of scabies manifesting as a disseminated erythematosquamous papular dermatosis. The lesions are evident in the trunk and in the right upper arm.

From the Department of Anatomical Pathology (Drs. Val-Bernal, González-Vela and Mira), and Services of Dermatology (Dr. Yáñez) and Rheumatology (Drs. Martínez-Taboada and Rodriguez-Valverde), Marques de Valdecilla University Hospital, Medical Faculty, University of Cantabria, Santander, Spain.

Address reprint requests and correspondence to Dr. Val-Bernal: Departmento de Anatomía Patológica, Hospital Universitario Marqués de Valdecilla, Avda. Valdecilla 1, 39008, Santander, Spain.

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1:100) for T-lymphocytes; CD20 (monoclonal, Dako, 1:50) for B-lymphocytes; CD68 (KP1, monoclonal, Dako, 1:25) for macrophages; and carcinoembryonic antigen (CEA, polyclonal, Dako, 1:500) for neutrophils.

Pathologic Findings

Two punch biopsy specimens of the erythemato-squamous papules were obtained from the abdomen and left leg, respectively. Histologic examination revealed a slightly acanthotic epidermis with focal parakeratosis, intracorneal pustules, and a mite of scabies in a burrow within the epidermal cornified layer (Figure 2). In the superficial dermis, there was a perivascular inflammatory infiltrate of mixed cell type with mononuclear cells, mainly macrophages, a few lymphocytes, neutrophils, and sparse eosinophils (Figure 3). Serial sections were required to demonstrate eggs and mites. Immunohistochemical stains showed that macrophages were the predominant cells in the infiltrate. Fewer T-lymphocytes and very few B-lymphocytes and neutrophils were detected.

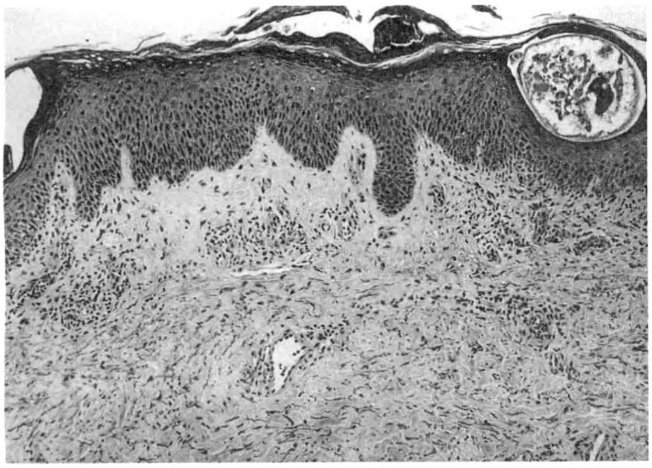

FIGURE 2. Papular lesion of scabies showing a scale-crust composed of parakeratotic cells and eosinophilic material, a scabie egg residing in the stratum corneum (on the left), and an adult mite within a subcorneal burrow (on the right). A mixed-cell perivascular infiltrate is present in the dermis (H&E, 25x).

Discussion

In classic scabies, the lesions are few and roughly symmetrical. These are frequently eczematous and occur in the hands, flexor surface of the wrists, elbows, and the anterior axillary folds. Other typical locations are female breasts, around the umbilicus, penis, and lower portion of the buttocks. However, there are special forms of scabies resulting in unusual clinical presentations, atypical locations and unusual extension of the disease closely simulating other entities. Some unusual forms of scabies are the crusted (Norwegian) scabies and the atypical (exaggerated) scabies.[2] In many cases of these unusual forms, the pruritus of classic scabies lessens or disappears, the sites of involvement are different, i.e., the scalp, face, back, and nails, and burrows are less apparent. It has been said that scabies is a great imitator. Thus, it can masquerade as psoriasiform dermatosis, contact dermatitis, Darier disease, dermatitis herpetiformis, bullous pemphigoid, malignant lymphoma, and systemic or cutaneous lupus erythematosus,[1] among other entities.

Crusted scabies has been associated with a wide group of disorders, including mental retardation, diabetes mellitus, and immunosuppressed status. New features associated with severe *Sarcoptes scabiei* infestations exist. Severe forms of infestation develop preferentially in cases of imbalance in host-parasite relationships. Immune deficiency is one etiologic factor that is being increasingly recognized. Forms of scabies associated with congenital, acquired or iatrogenic suppression of the immune response

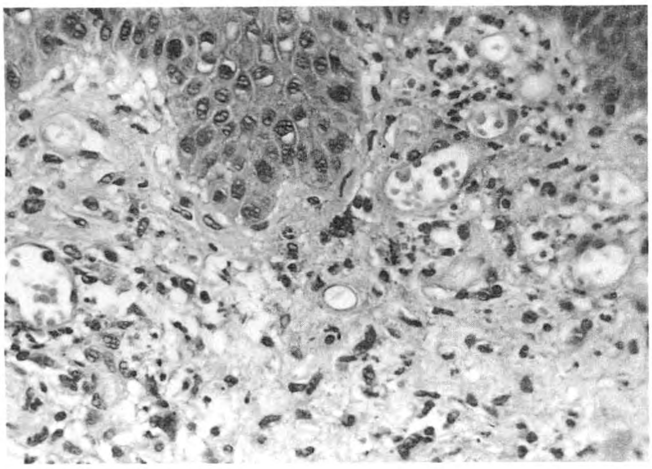

FIGURE 3A. The inflammatory-cell infiltrate consists of histiocytes, lymphocytes, and neutrophils arranged around blood vessels of both superficial and deep plexuses (H&E, 80x).

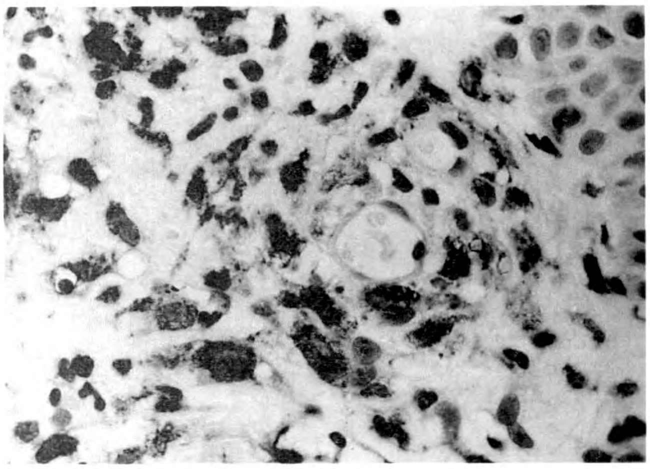

FIGURE 3B. Monoclonal antibody CD68 (KP1) decorating the cytoplasm of most of the cells of dermal infiltrate (160x).

include the following: 1) spontaneous essential immunodeficiency with *Pneumocystis carinii* infection in patients who do not have acquired immune deficiency syndrome (AIDS);[3] 2) HTLV-I-associated T-cell leukemia;[4] 3) HTLV-III infection (AIDS);[2] 4) lepromatous leprosy;[5] 5) dialysis with or without immunosuppression;[6] 6) corticosteroid therapy, including topical treatment;[7] 7) renal transplantation;[8] 8) bone marrow transplantation;[9] 9) Bloom's syndrome;[10]; and 10) SLE.[11-16]

Scabies has rarely been described in patients with SLE. A review of the literature revealed eleven reported cases.[11-16] Scabies in these eleven cases appeared to be more severe than usual, and seven of the patients developed crusted scabies. Atypical or exaggerated type of scabies was observed in only four patients.[11,13]

An exaggerated form of scabies with generalized papulosquamous lesions occurred in our patient upon treatment for SLE. This special form can be designated scabies incognito, as the lesions were ascribed to SLE. In our case, systemic and topical corticosteroid therapy aggravated a primary cutaneous involvement, resulting in a severe form of infestation. The role of immunologic mechanisms in limiting the number of scabies mites is not well defined. However, the cellular immunity of the host appears to play a significant role.[17] Histology suggests that a cell-mediated reaction causes the lesions of classic scabies. Lymphocytes constitute the majority of cells in the inflammatory infiltrate and T-cells dominate.[17] The ratio of T-cells to B-cells in the lesions is greater than in the peripheral blood.[18] This suggests a selection of T-lymphocytes in the inflammatory infiltrate. SLE is characterized by an alteration of humoral and cellular immunity,[19] with loss of suppressor T-cell function.[20] Corticosteroid therapy decreases T-cell response. It is not surprising, therefore, that in our case macrophages were predominant in the infiltrate. The exaggerated form of scabies in the present case may be the result of underlying SLE and oral and topical usage of corticosteroids. Secondary bacterial infection may complicate scabies. The mite scybala and the fissures probably contribute to bacterial colonization.

It is necessary to emphasize the importance of a rapid diagnosis of scabies and that of the secondary bacterial infection, because four patients reported with this complication in SLE died of septicemia.[12,13,15,16] These patients had developed crusted scabies.

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IMPETIGO HERPETIFORMIS: AN OBSTETRIC CONCERN

Ekuma N. Ekuma-Nkama, MB, FRCOG, FICS; Vibha K. Garg, MB, FRCOG;
Mohammed Al Khars, MD, FRCPC

Impetigo herpetiformis, a very rare form of pustular psoriasis occurring in pregnancy, is potentially serious and aggressive treatment is usually required. We report a case of a patient presenting with two consecutive pregnancies complicated by impetigo herpetiformis. The disease appeared much earlier than the classic third trimester presentation. The first pregnancy was induced because of worsening symptoms, while the second pregnancy ended in a stillbirth. Early diagnosis and treatment of impetigo herpetiformis is essential to reduce both maternal and fetal morbidity and mortality.

Case Report

A 27-year-old primigravida presented at 19 weeks' gestation, complaining of a papular skin eruption for the previous three months. This was diagnosed as psoriasis. The patient gave no family history of any skin conditions. At 36 weeks, she presented with a one-week history of malaise, fever, leg pains and worsening of the previously noted generalized skin eruption.

On examination, large circinate lesions with superficial pustules at the periphery and central desquamation were noted, mostly on the legs. Some scattered papules, pustules and psoriatic lesions were seen on the elbow and abdomen. A clinical diagnosis of impetigo herpetiformis, also called generalized pustular psoriasis of pregnancy, was made and treatment was commenced with Eucerine cream and oral dosage of 40 mg prednisolone daily. Two biopsies taken from the lesion showed acanthosis, parakeratosis and intraepidermal pustules filled with numerous neutrophils. The immunofluorescence studies were negative for IgG, IgM, IgA, C_3 and fibrinogen. Blood studies showed a leukocytosis of $13.2\text{x}10^9$/L (normal range $5\text{-}10\text{x}10^9$/L) and mild hypocalcemia of 2 mmol/L (normal range 2.2-2.625 mmol/L). In spite of the treatment, the lesions got worse, and so labor was induced at 38 weeks, with the delivery of an infant weighing 3.020 kg, with Apgar scores of 6 and 8 at 1 and 5 minutes, respectively.

Two days postpartum, the lesions began to improve and the patient was discharged home on 5-fluorouracil cream and clobetasol propionate ointment. When she was seen two weeks later, there was a marked improvement in her condition, although new pustular lesions were still appearing. The prednisolone therapy was re-commenced at 40 mg/day for one week, and the dose was gradually reduced over the next four weeks to 5 mg daily. There was some improvement, but since new lesions were still appearing, methotrexate 5 mg once/week orally was commenced and gradually increased to 20 mg weekly. Serial CBC and hepatic panel were performed weekly and vitamin D 50,000 IU daily and vitamin E were given as supplements for three months postpartum. The lesions resolved completely during this period, so methotrexate and prednisolone were gradually tapered off over the next three months.

At six months postpartum, all lesions had cleared completely, except for some mild postinflammatory pigmentation. Immediately after discontinuing the treatment, the patient became pregnant again. She had a recurrence of the extensive pustular lesions at 16 weeks, and treatment with prednisolone had to be started again.

At 32 weeks' gestation, the patient had a fetal biophysical profile which was normal. Unfortunately, she presented 12 days later with an intrauterine fetal death. She had a normal vaginal delivery of a stillborn infant weighing 1.820 kg.

Discussion

Impetigo herpetiformis is a very rare form of pustular psoriasis, which arises suddenly in a patient with no personal or family history of psoriatic skin disease. It usually occurs during pregnancy in the third trimester, but may occur as early as the third month.[1] It is potentially serious and aggressive treatment is usually required.[2]

The eruption consists of urticarid erythema which begins in the flexures, especially in the inguinal region, with superficial pustules arranged in rings or groups at the margins of the lesion. The lesions spread gradually until the entire body is involved, except for the face, hands and

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From the Departments of Obstetrics and Gynecology (Drs. Ekuma-Nkama and Garg), Al-Hasa Specialty Services Division, and Dermatology (Dr. Al-Khars), Al-Hasa Medical Services Division, Saudi Aramco Medical Services Organization, Mubarraz, Saudi Arabia.

Address reprint requests and correspondence to Dr. Ekuma-Nkama: Al-Hasa Specialty Services Division, Saudi Aramco-Al Hasa Health Center, P.O. Box 6030, Saudi Aramco, Mubarraz 31311, Saudi Arabia.

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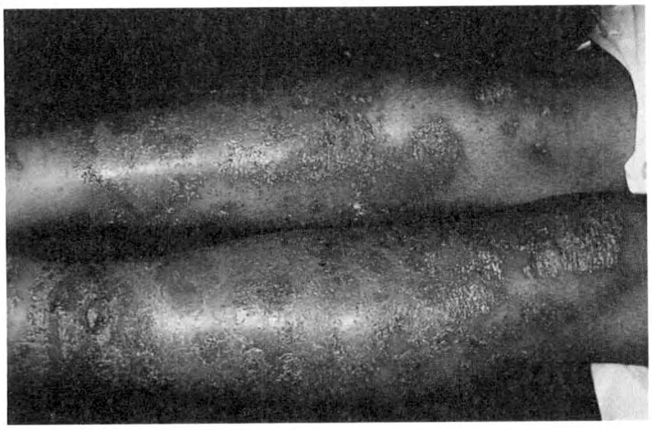

FIGURE 1. Lower limbs: extensive areas of erythema, maceration and pustules.

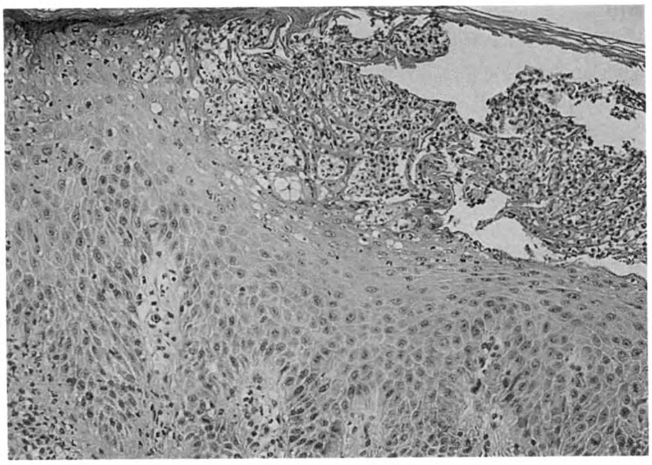

FIGURE 2. High-power micrograph: featuring subcorneal intraepidermal pustule.

feet. As the pustules break down in the central area, crusting and impetiginization result.

The skin eruption is accompanied by fever, malaise, delirium, nausea, diarrhea and vomiting, neutrophilia, elevated erythrocyte sedimentation rate, hypocalcemia and tetany. Severe dehydration, prostration and convulsions have been reported. Pruritus is generally not a problem and lesions gradually heal without scarring, unless infected or excoriated. Postinflammatory hyperpigmentation is regularly seen. Histology is similar to that of pustular psoriasis, with spongiform pustules of Kogoj and perivascular infiltrates within a focus of spongiotic epidermis. Direct and indirect immunofluorescence findings are negative.

The treatment of choice in pregnancy is prednisone 15-30 mg/day. Cyclosporine, a cyclic polypeptide immunosuppressant agent, is an effective drug for treating psoriasis. It is fetotoxic in animal studies at high doses. No adverse effects have been reported in the human fetus, however, there are no adequate and well-controlled studies in pregnant women. It should, therefore, be used only if the potential benefits justify the potential risk to the fetus. Although etretinate, an oral retinoid, and methotrexate, an antineoplastic agent, are the drugs of choice in the treatment of pustular psoriasis, they are not used in pregnancy because of their embryotoxic side effects. Antibiotics can be added if there is secondary infection. Fluid and electrolyte balance should be maintained and hypocalcemia corrected. As the fetal mortality is high, even when the disease appears well controlled with corticosteroids, fetal well-being should be monitored using biophysical profile and umbilical artery Doppler studies.

If fetal or maternal conditions deteriorate, pregnancy should be terminated by induction of labor or Cesarean section, as indicated. Maternal mortality is now uncommon, but stillbirth and intrauterine growth retardation may occur even when the disease appears to be controlled with corticosteroids.[3]

Low-dose methotrexate can be substituted in the postpartum period to prevent rebound of rashes, but is contraindicated in pregnancy and lactation. The disease remits after delivery but may recur in successive pregnancies.

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PULMONARY HEMOSIDEROSIS IN AN INFANT WITH PSORIASIS

M. Alshehri, MBBS, FRCPC

Generalized pustular psoriasis (GPP) is an acute inflammatory dermatosis typically associated with systemic features, such as fever, arthralgia, leukocytosis, diarrhea, and altered liver function. It is relatively rare, although onset in infancy has been described.[1-2] GPP has also been reported in association with chronic, recurrent, multifocal osteomyelitis (CRMO) in the first few months of life.[3] Cardiorespiratory failure is reported as the most common cause of death in patients with erythrodermic dermatoses, including GPP, where mortality approaches 70%.[4] We describe an infant who developed lytic bone lesions, GPP and pulmonary involvement in the form of pulmonary hemosiderosis.

Case Report

A 21-month-old male was born at 36 weeks' gestation to a 28-year-old gravida two para one mother. He presented at our hospital with a stormy clinical course that included chronic skin rash, lytic bone lesions, chronic respiratory symptoms and a past history of birth asphyxia and hypotonia.

A generalized skin rash, involving the scalp, trunk, and limbs and associated with nail pitting and swelling over his joints, appeared in the first few months of life. The patient subsequently developed chronic respiratory symptoms, including tachypnea, wheeze, cough, and chest indrawing. The relevant physical findings included tachypnea, intercostal and subcostal retraction, decreased air entry at the lung bases with crackles and occasional wheeze, hepatomegaly, and generalized pustular rash (see before and after photographs, Figure 1). His chest x-ray revealed both air space and interstitial patterns. Feeding study revealed a lack of swallowing coordination and aspiration of liquids, and skeletal survey revealed soft tissue swelling and lytic lesions over the distal femora, proximal and distal tibia, and over the ribs and vertebrae (Figure 2). Later, x-rays showed healing of some of these lesions. Abdominal ultrasound showed coarse liver appearance without focal changes, a normal spleen and no adenopathy. Infectious work-up, including bone samples for fungi, tuberculosis and other bacteria, were all negative. Mantoux and VDRL tests were negative. The immunological work-up showed normal immunoglobulin levels, T- and B-cell populations, and normal day 3 and day 6 lymphocyte proliferation studies. Neutrophil studies showed impaired chemotaxis but normal phagocytosis, killing test, nitroblue tetrazolium reduction, and skin window.

Other laboratory investigations, including repeated CBC, liver function enzymes, BUN, creatinine, and electrolytes, did not reveal major abnormalities, apart from chronic normocytic anemia.

The patient's clinical course was complicated mainly by skin rash exacerbation, occasionally associated with skin infection. He also continued to have frequent exacerbation of his respiratory symptoms, which led to several hospital admissions, including the Intensive Care Unit, resulting in several episodes of intubation. He was initially treated with salbutamol, ipatropium promide, pulmicort and antibiotics, mainly at the time of respiratory exacerbation. His skin condition was treated initially with

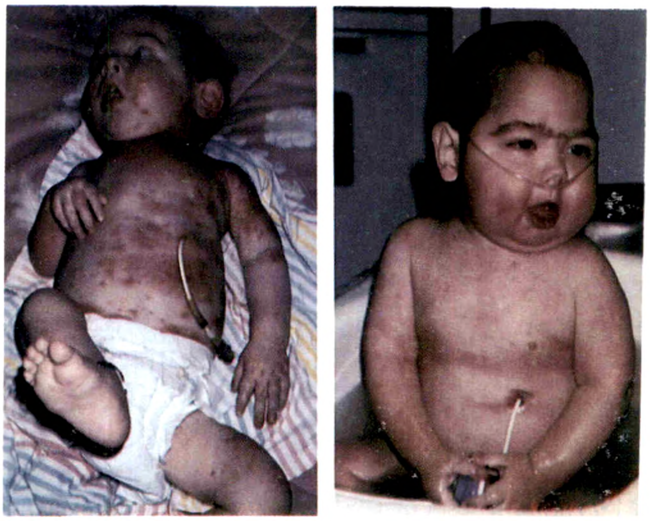

FIGURE 1. Patient photo showing skin involvement: Left: before, and, right, after treatment.

From the Department of Pediatrics, College of Medicine, King Saud University, Abha Branch, Abha, Saudi Arabia.

Address reprint requests and correspondence to Dr. Alshehri: Department of Pediatrics, College of Medicine, King Saud University, Abha Branch, P.O. Box 641, Abha, Saudi Arabia.

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topical steroids and systemic antibiotics at times of skin infection. Skin histology excluded histiocytosis X, and favored pustular psoriasis, with aseptic subcorneal pustules and mild acanthosis (Figure 3). The patient was then treated more aggressively with systemic steroids, improving both his skin rash and respiratory status with decreased oxygen requirement and less frequent exacerbation of the generalized pustular rash.

To determine the nature of his lung involvement, the patient underwent open lung biopsy, which showed some pleural and septal fibrosis, type 2 pneumocyte hyperplasia, and prominent alveolar exudate of hemosiderin-laden macrophages. No vasculitis was present and immunofluorescence staining for immunoglobulins and C3 complement were negative, and no organisms were identified. He was then maintained on a regimen of steroids and cyclosporin, which led to control of his skin lesions and less frequent respiratory exacerbations. Other maintenance treatment included Fer-In-Sol, cisapride, gastrostomy tube feedings, and 0.250 L/min. oxygen.

At the age of 28 months, the patient refused to be seated upright. CT scan and magnetic resonance imaging of the spine revealed a prevertebral mass at the level of the 7th and 8th thoracic vertebrae. The CT scan-guided biopsy was inconclusive, and he underwent an open biopsy that showed aseptic osteomyelitis with periosteal fibrosis and new bone formation.

Discussion

Pulmonary hemosiderosis has been reported in some cases with an immune etiology[5] associated with collagen vascular diseases, or as an early manifestation of a systemic vasculitis.[6]

Previous reports of pulmonary inflammation coincident with generalized pustular psoriasis[7,8] were diagnosed as sterile pneumonitis or unexplained alveolar shadowing on x-ray. Recently, three adult cases of GPP complicated by profoundly increased pulmonary capillary permeability (capillary leak syndrome) have been described.[9,10] It has been proposed that pulmonary inflammation coincident with extensive cutaneous disease might result from the action of epidermal cell-derived inflammatory mediators on the pulmonary vasculature.[9]

Psoriasis is a chronic skin disease characterized histologically by prominent keratinocyte (KC) hyperplasia and an early inflammatory-cell infiltrate that predominantly includes T-lymphocytes and macrophages.[11] In vivo studies[12] have shown an important coordinated interaction between tumor necrosis factor-alpha-producing dermal dendrocytes and overlying KCs, which have increased expression of interleukin 8 (IL-8), intercellular adhesion molecule 1 (ICAM-1), and transforming growth factor-alpha (TGF-α). Furthermore, increased serum levels of tumor necrosis factor-alpha (TNF-α) were found in a patient with psoriasis,[13] suggesting that cytokines synthesized by KCs are released into the circulation during cutaneous inflammation. Cytokines are important mediators of pulmonary inflammation.[14] This immune-mediated mechanism was proposed by McGregor and colleagues[9] to be the probable cause of the development of increased pulmonary vascular permeability in their two patients. We speculate that this immune-mediated mechanism might also account for alveolar hemorrhage in our case. The hemorrhage appeared coincident with exacerbations of GPP, leading to recurrent respiratory symptoms in our patient. Glucocorticosteroids are efficacious in a wide variety of

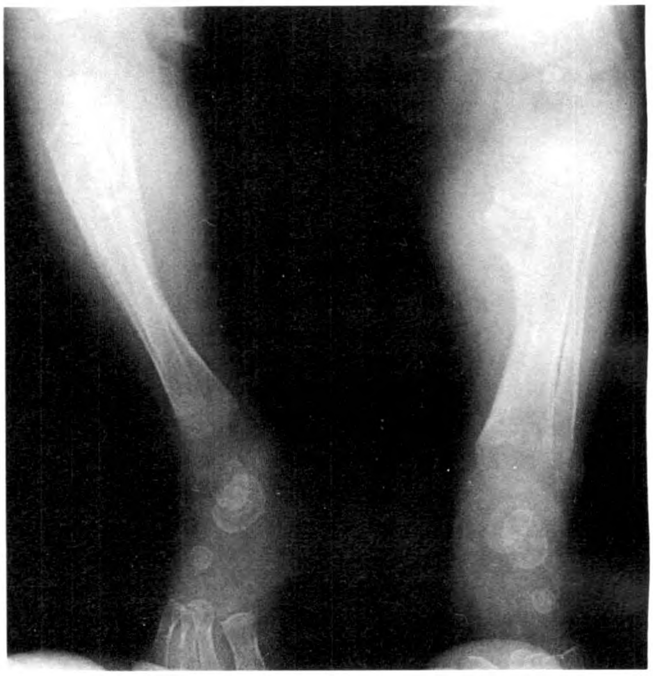

FIGURE 2. Bone x-ray showing lytic lesions.

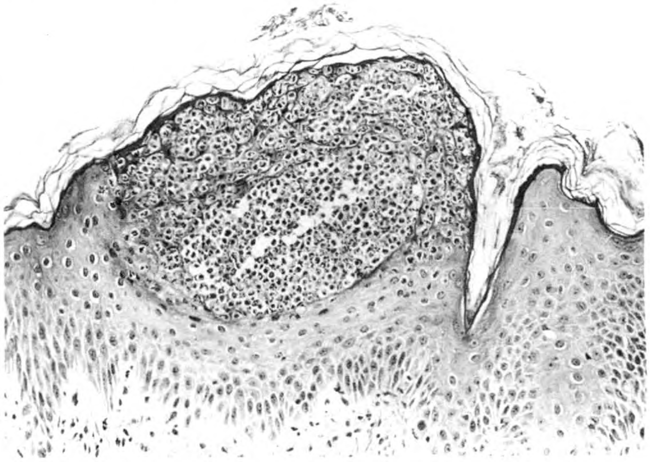

FIGURE 3. Skin biopsy showing subcorneal pustule (H&E, 250x).

inflammatory skin diseases with multiple etiologies. The suggested logical explanation for their action is that they block production of pro-inflammatory cytokines, adhesion molecules and chemotoxins by KCs and immunocytes.[15]

The patient's respiratory symptoms and chest x-ray findings, as well as his skin disease, improved with steroid treatment. Unfortunately, the patient developed systemic steroid side effects, requiring substitution with cyclosporine. This regimen also led to control of both his respiratory symptoms and skin disease. Cyclosporine A can improve psoriasis[16] because this compound has been shown to inhibit TNF-α production.[17]

Interestingly, in the long-term follow-up of our patient, the pulmonary disease paralleled that of the GPP. Respiratory symptoms would appear at the times of flare-ups of the pustular psoriasis. The patient is maintained mainly on cyclosporine and a short course of steroids is added at the time of exacerbations.

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SIRENOMELIA WITHOUT VITELLINE ARTERY STEAL

F. Jaiyesimi, FRCP; T. Gomathinayagam, DMRD;
A. Dixit, MD; M. Amer, MD

Sirenomelia sequence is a rare malformation, the reported incidence being 1.5-4.2/100,000 births.[1] It is characterized by the presence of a single lower limb (simpus), which may have two feet (simpus dipus), one foot (simpus monopus), or no recognizable foot (simpus apus). The lower limb may be oriented anteriorly[2] or posteriorly.[3]

Current interests in the malformation center on its relationship to VACTERL (vertebral, anal, cardiovascular, tracheal, esophageal, renal and limb) association and its pathogenesis, particularly the reported role of a "vitelline artery steal,"[4] vis-a-vis a primary defect in the formation of the caudal mesoderm and related structures.[5,6] We report here a case which is remarkable in two aspects: 1) its very close similarity to VACTERL and more importantly, 2) the absence of a demonstrable arterial steal.

Case Report

The infant was born after 35 weeks of unsupervised pregnancy to a healthy 26-year-old gravida 7, para 6 mother. Delivery was by assisted breech. Apgar scores were 4 at one and 8 at five minutes, and both the birthweight (1740 g) and length (43 cm) reflected intrauterine growth retardation. The parents, who are not consanguineous, have five healthy children, and knew of no family history of malformations. Immediate postnatal examination revealed a severely malformed baby. There were features of Potter sequence, including retrognathia, hypertelorism, medial epicanthic folds, and rudimentary ears with no auditory meatus. Copious secretions poured out persistently from his mouth and nostrils, raising a suspicion of esophageal atresia. Cardiac evaluation was normal, but the umbilical cord contained only one artery. The anus and external genitalia were absent; only a 3x8 mm skin tag marked the position of the genitalia. Neither the urinary bladder nor the kidneys were palpable. This, in the setting of absent urethral opening, raised a suspicion of renal agenesis.

There was a single lower limb, but with two feet fused posteriorly. It was anteriorly oriented and held at fixed flexion relative to the trunk (Figure 1). Radiographs revealed that it contained the complete pairs of lower limb bones. Both hips were dislocated, and the sacrum pointed posteriorly.

Other malformations ascertained after further investigations included esophageal atresia with tracheo-esophageal fistula and duodenal atresia. Abdominal ultrasonography failed to demonstrate any internal genitalia, bladder or kidneys. The diagnosis of bilateral renal agenesis was further confirmed by the failure to demonstrate any dye excretion after intravenous urography. Echocardiography was normal, as was cranial ultrasonography.

Aortography, performed through an umbilical artery catheter, revealed tapering of the aorta along its course. It measured 9 mm at the level of T_4, 7 mm just above the diaphragm, and 5 mm at its bifurcation which, however, occurred normally at the level of L_4. The celiac artery appeared small and was poorly opacified. The renal and inferior mesenteric arteries were absent, while the other branches of the abdominal aorta appeared attenuated

TABLE 1. *Main defects in caudal regression syndrome (CRS), VACTERL association and sirenomelia sequence.*

Type or location of defect	Relative frequency (%) CRS (N 153)[10]	VACTERL (N 120)[10]	Sirenomelia (N 134)*	Present patient
Vertebrae/sacrum/pelvis	100	100	100	+
Lower limb	73	30	100	+
Anorectal	0	88	97	+
Renal	26	85	93	+
Genital	3	55	85	+
Lower urinary tract	0	48	57	+
Single umbilical artery	0	10	79	+
Cardiac	0	24	26	–
Radial limb	0	29	21	–
Esophageal atresia ±TOF	0	28	5	+
Other GI defects	0	21	44	+
Respiratory tract (excluding TOF)	0	11	24	–
CNS	69	16	8	–

*Based on data from Duncan et al. (54 patients),[10] and Stocker and Heifetz (80 patients);[1] TOF=tracheo-esophageal fistula.

From the Departments of Pediatrics (Drs. Jaiyesimi, Dixit and Amer), and Radiology (Dr. Gomathinayagam), Buraimi Hospital, Buraimi, Sultanate of Oman.

Address reprint requests and correspondence to Prof. Jaiyesimi: P.O. Box 377, Code 512, Buraimi, Sultanate of Oman.

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(Figure 2). The single umbilical artery, which was small as well, branched off normally from the right iliac artery at the level of L_5.

The baby succumbed on day 5. Cultural constraints precluded an autopsy.

Discussion

Duhamel coined the term "caudal regression syndrome" in 1961 to describe the association of sirenomelia with anorectal, genitourinary, and vertebral anomalies.[7] Later, a distinction was made between sirenomelia sequence and caudal regression syndrome in the belief that the former had a specific pathogenetic factor, namely arterial steal, whereas the latter was probably a heterogenous group with diabetic embryopathy as the single most frequently suspected etiological factor.[8]

In 1973, Quan and Smith[9] proposed the acronym VATER to denote the non-random association of vertebral defects, tracheo-esophageal fistula with esophageal atresia, renal and radial limb defects. It was suggested that categorization as VATER required the presence of at least three of these defects. The acronym was later expanded to VACTERL in order to reflect the importance of associated cardiac and non-radial limb defects.

Lately, some authors have drawn attention to the overlap in the phenotypic manifestations of sirenomelia sequence and VACTERL.[10-12] Some idea about the extent of the overlap can be gleaned from Table 1, which we compiled by rearranging data from two major publications on these malformations.[1,10] In the series by Stocker and Heifetz,[1] all 80 sirenomelics had at least three other VACTERL anomalies in addition to the limb defect. Similarly, 48 of the 50 sirenomelics analyzed by Duncan et al.[10] had at least three of the six VACTERL ascertainment anomalies. Our patient had four VACTERL anomalies, excluding the simpus. It seems, therefore, that in most cases, the difference between sirenomelia sequence and VACTERL lies mainly in the severity of the component defects, with the single lower limb in sirenomelia being an epitome of other severe malformations, especially in the gastrointestinal and genito-urinary systems.

The etiology of sirenomelia sequence is uncertain, as no specific teratogens have been associated with the malformation in humans. However, an association with twinning is suspected. Its incidence is 100-150 times higher in monozygotic compared with dizygotic twins or singletons, and close to 20% of the reported cases were in products of twin pregnancies.[1,11,13]

In view of the strong association between caudal regression syndrome and maternal diabetes mellitus,[8,14,15] reports of sirenomelia in infants of diabetic mothers have aroused suspicion of a causal relation between the two diseases.[15] However, a critical review of the literature shows that only 0.5%-3.7% of cases of sirenomelia occurred in offspring of diabetic mothers,[1,11,15] meaning that the association between maternal diabetes and sirenomelia is, at best, weak.

An inherited form of caudal dysgenesis has been recognized,[16] and a few cases have also been attributed to aneuploidies, including trisomies 13 and 18, and 6q and 13q deletions.[5] To date, however, there is no evidence of a genetic basis for sirenomelia sequence.

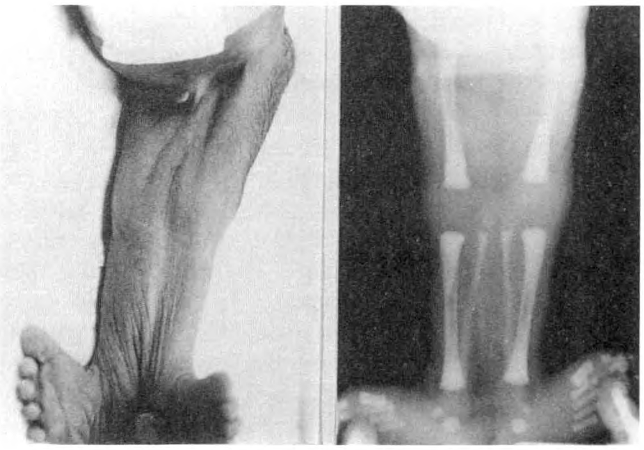

FIGURE 1. Composite illustration of the lower extremity in infant with sirenomelia. Left panel shows the fused lower limb with two feet (sympus dipus), but a radiograph of the limb (right panel) revealed that it contained the complete set of lower limb bones.

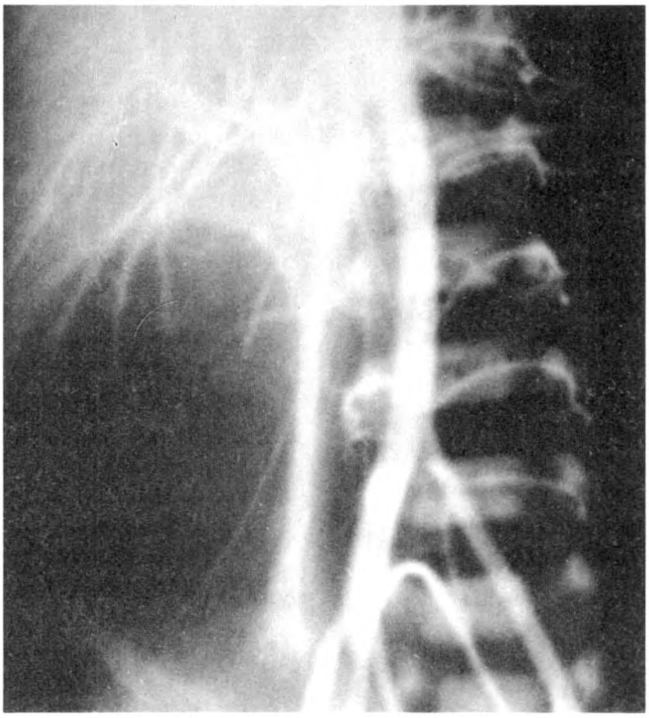

FIGURE 2. Transumbilical aortogram: the abdominal aorta tapers distally but remains the dominant artery. The inferior mesenteric and renal arteries are absent while the other branches of the abdominal aorta are attenuated and poorly opacified. The single umbilical artery (catheterized) arises from the right iliac artery at the level of L_5; it, too, is attenuated.

Like its etiology, the pathogenesis of sirenomelia sequence is also uncertain, and speculations on this theme are almost as varied as the clinical spectrum of the disease. In 1987, Stocker and Heifetz[1] summarized the theories proposed thus far. The most plausible among them were: 1) a defect in the primitive streak with subsequent malformation of the caudal region; 2) neural tube distension in the caudal region with lateral rotation of the mesoderm resulting in fusion of the hind limb buds; and 3) a defect of the midline structures, including cloacal and urogenital sinus derivatives, which allows approximation and fusion of the hind limb buds.

At about the same period, Stevenson et al.[4] proposed the "vitelline artery steal" theory. They reported that in each of 11 sirenomelia specimens which they had studied, a large artery, presumed to be a derivative of the vitelline artery, arose from the aorta high in the abdominal cavity, beyond which point the aorta and its branches were hypoplastic. They stressed that "the major abdominal artery is, without exception, a derivative of the vitelline artery complex," and inferred that sirenomelia resulted from a "vitelline artery steal," which diverted blood and nutrients away from the caudal portion of the embryo to the placenta. That inference met with wide, but not unanimous, acceptance.[2,3,5,8,17]

Earlier, Heifetz,[18] reporting on a group of 25 sirenomelics in whom the umbilical cord was examined, stated that each had a single umbilical artery, which arose directly from the aorta just distal to the celiac axis. He suggested that the high origin of the single umbilical artery was unique to sirenomelia.

A different arterial pattern was noted in our patient. Although the aorta tapered along its course, it remained the major artery throughout. All its branches, including those derived from the vitelline artery (namely, celiac and mesenteric arteries), showed severe degrees of attenuation. In addition, the single umbilical artery arose normally from the iliac artery and, unlike those in the specimens studied by Stevenson et al.,[4] it was not a large vessel. Clearly, that pattern is not consistent with a vitelline artery steal. On the contrary, the extremely small caliber of the celiac and mesenteric arteries suggests that the vitelline artery complex itself was hypoplastic.

Experimental studies have also been conducted with a view to ascertaining the pathogenesis of sirenomelia and related malformations. Recently, Alles and Sulik[5] produced caudal dysgenesis in mouse embryos by exposing them to etretinate (a synthetic vitamin A analogue and potent teratogen) on the eighth day of gestation. The defect seemed to have resulted from excessive cell death in the primitive streak and hindgut endoderm. Similarly, Wei and Sulik[6] produced sirenomelia, secondary to cell death in the caudal mesoderm, in chick embryos exposed to ochratoxin A (a fungal toxin) during organogenesis.

These laboratory findings, the absence of a demonstrable arterial steal in our patient, and the occurrence in many other patients of defects proximal to the territory of the abdominal aorta,[1,11,19] all suggest that factors other than vitelline artery steal can produce sirenomelia in humans. Excessive primary cell death in the caudal mesoderm and hindgut endoderm[5,6] seems to be one such factor. Axial mesodermal dysplasia and midline developmental field defects have also been suggested as plausible mechanisms, especially in patients with cephalic and caudal defects.[19]

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BOWEL INTUSSUSCEPTION IN A PATIENT WITH HUMAN IMMUNODEFICIENCY VIRUS INFECTION

Nermin Halkic, MD; Abdoulah Kayoumi, MD; François Mosimann, MD, PhD

Adult intussusception represents 5% of all intussusceptions and 1% of all bowel obstructions. In adults, it is often associated with a systemic disease, such as acquired immune deficiency syndrome (AIDS), and is usually caused by a focal pathologic process at the point of the intussusceptum. In these patients, diagnosis is often delayed, mainly because of the nonspecific and prolonged nature of the symptoms and because of the extensive differential diagnosis of nonsurgical abdominal conditions.[1,2] Leucocyte count is rarely increased because of the depressed immune response. We present here the case of a patient with AIDS, who developed an ileocolic intussusception after laparoscopic appendectomy. The clinical and radiographic findings are described.

Case Report

An HIV-positive 37-year-old woman, with a CD4 count of 150 cells per cubic millimeter, was admitted for abdominal pain associated with nausea and vomiting. Pain without rebound tenderness was maximal in the right lower quadrant. Her temperature was 37.8°C and leukocyte count was 12.5 g/L. The abdominal ultrasound was inconclusive. The patient underwent an exploratory laparoscopy that showed an inflamed appendix. Histology confirmed the diagnosis of acute appendicitis. She was discharged the following day but was readmitted 48 hours later, with a recurrent, incapacitating abdominal pain. On plain abdominal film, there were signs of a small bowel ileus. Intussusception was suggested on the CT scan by a typical target image, with low-attenuation mesenteric fat surrounded by high-attenuation bowel wall (Figure 1).[3] Ileocolic intussusception was confirmed at laparotomy. However, no pathologic lead point could be found. Reduction was possible without the need for resection. The patient recovered uneventfully.

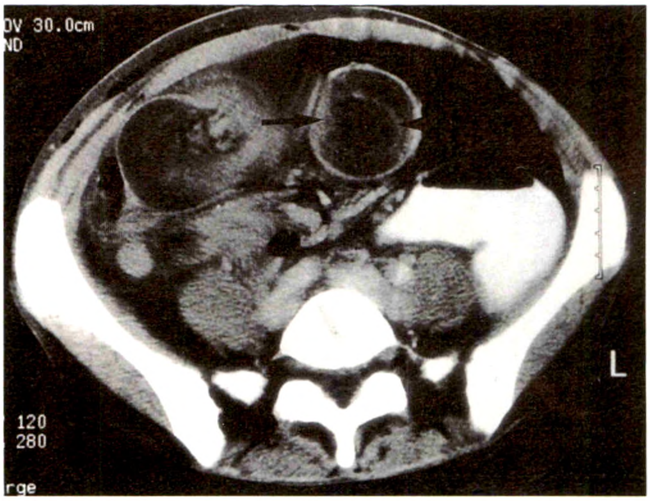

FIGURE 1. CT scan shows a typical target-shaped intussusception with low attenuation mesenteric fat (arrow) surrounded by high attenuation bowel wall.

Discussion

Intussusception is defined as the invagination of one segment of the bowel into another. Intraluminal tumors, submucosal edema, or any process that can cause dysrhythmic contractions of the bowel muscle may initiate an intussusception. In adults, colon intussusception is most commonly due to malignancy, while small bowel intussusception is more likely due to a benign tumor. A number of gastrointestinal manifestations of AIDS, including lymphoma, cytomegalovirus colitis or Kaposi's sarcoma can also potentially initiate an intussusception.

The radiologic signs of intussusception on CT scan are very specific. The distended loop of bowel (called the intussuscipiens) has an apparent thickened wall that actually consists of two layers of bowel resulting from the invagination of the intussusceptum. The intussusceptum usually occupies an eccentric position, being displaced by the attached mesentery to the antimesenteric side. The image may sometime suggest other causes of bowel wall thickening, such as ischemia, neoplasm or inflammatory bowel disease,[4] but contrast enhancing of the mesenteric vessels supports the diagnosis.

From the Department of Surgery, University of Lausanne Medical School, Lausanne, Switzerland.

Address reprint requests and correspondence to Dr. Halkic: Department of Surgery, University of Lausanne Medical School, CH-1011 Lausanne-CHUV, Switzerland.

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Patients with AIDS are at risk for a number of small bowel processes that may act as lead points for intussusception. Among these are the numerous types of hypersecretory infectious enteritis to which AIDS patients are prone, and that can cause intrinsic small bowel inflammation and lymphoid hyperplasia.[5] A motility dysfunction of neuroendocrine origin has been proposed as a mechanism of intussusception in those cases where no lead point could be found.[6] In our patient, no pathological process could be demonstrated. It is unclear, however, whether the suggested motility dysfunction was associated with an AIDS-related neuroendocrine disorder, or to the close proximity of the resected appendix to the intussusception site.

AIDS-associated intussusception in the adult is an entity with an unknown frequency. The condition may be more common than clinically appreciated and requires a high degree of suspicion, given the scope of abdominal pathologies susceptible to producing intermittent abdominal colicky pains in AIDS patients. CT scan is helpful in diagnosing intussusception and should be obtained in AIDS patients with violent abdominal pain of unclear origin.

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A RARE CASE OF NEONATAL ALLOIMMUNE THROMBOCYTOPENIA DUE TO ANTI-HPA-2b

Iman H.A. Al-Sheikh, MBBS, DCP, FCP; Mohammed Khalifa, MSc;
Amjad Rahi, MD, FRCPath; Mohammed I. Qadri, MD, PhD; Kamel Al Abad, MBBS

Despite the fact that neonatal alloimmune thrombocytopenia (NAIT) is a relatively rare disease (1/1500-1/5000 live births),[1] its importance stems from its potential to cause serious complications. NAIT accounts for 20% of cases of neonatal thrombocytopenia and is most commonly attributed to platelet-specific antigens. Diagnosis is usually confirmed by demonstrating that antiplatelet antibodies in the mother's serum are reactive with her baby's or husband's platelets. This test is, however, not always reliable.[2] Alternatively, platelets from the family could be serotyped, using specific antisera, but this is usually limited to reference laboratories. Recently, it has become possible to genotype platelet alloantigens, using various DNA-based techniques.[3,4] This does not only simplify diagnosis but also allows early recognition and therapeutic intervention, such as intrauterine platelet transfusion and delivery by cesarean section. These therapeutic measures may prevent mortality or serious sequelae, such as permanent CNS damage. In this case report, we discuss the utilization of polymerase chain reaction–sequence specific primer (PCR-SSP) technology in a Saudi newborn with NAIT.

Case Report

A full-term, low birth weight (2.3 kg) baby boy was normally delivered in the Maternity and Children's Hospital, Dammam in 1997. Apgar score was normal and there were no dismorphic features, petechiae or purpuric lesions. Routine biochemical investigations revealed low serum glucose (34 mg/dL). Hematological tests done on the first day showed normal Hb 21.1 g/dL, normal WBC (8.5×10^9/L) and low platelet count (100×10^9/L). The platelet count thereafter dropped to 66×10^9/L on the 6th day of admission and became normal (163×10^9/L) two weeks after delivery. Differential WBC count showed a predominance of lymphocytes (54%), with 42% neutrophils, 2% monocytes and 2% eosinophils. Apart from a few nucleated RBC and physiological macrocytosis, RBC morphology was normal. A few platelets looked morphologically large. Coagulation studies excluded disseminated intravascular coagulopathy (DIC). Serological evaluation was negative for toxoplasma, but positive (IgG) for both rubella and cytomegalovirus (CMV), indicating maternally acquired antibodies. Blood culture did not grow any bacteria. The mother had three other healthy children. She aborted twice during her second and fourth pregnancies in the first and second trimesters for unknown etiology. She had a history of hypertension but was not on any medication. There was no history of a similarly affected sibling with thrombocytopenia or bleeding manifestations. The mother herself did not have any history of bleeding. Her platelet count was 216×10^9/L on the day of the delivery.

Detection of Anti-Platelet and Anti-HLA Antibodies

Serum was collected from the baby and the mother, and 10 mL EDTA blood from the father provided platelets for the antibody test. Platelet indirect immunofluorescent test (PIFT) was performed by the recommended technique.[5] The father's platelets were incubated in one tube with the maternal serum and in another tube with the infant's serum. A second layer of fluorescein isothiocyanate-labelled mouse anti-human IgG was added. Slides were examined under the epifluorescence microscope using FITC interference filter. A control normal serum was run with the father's platelets in parallel. This test revealed that maternal serum contained an alloantibody which reacted with the father's platelets.[1]

TABLE 1. *HPA 1-5 genotype of the family.*

	HPA genotype		
HPA system	Father	Son	Mother
HPA-1	ab	aa	ab
HPA-2	ab	ab	aa
HPA-3	aa	aa	aa
HPA-4	aa	aa	aa
HPA-5	aa	aa	aa

From King Faisal University (Dr. Al-Sheikh), the Regional Laboratory and Blood Bank (Drs. Rahi, Qadri and Mr. Khalifa), and the Maternity and Children's Hospital (Dr. Abad), Dammam, Saudi Arabia.

Address reprint requests and correspondence to Dr. Al-Sheikh: Consultant Hematologist and Assistant Professor, King Fahad Hospital of the University, P.O. Box 30500, Al-Khobar 31952, Saudi Arabia.

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TABLE 2. *Estimated risk of NAIT-complicated pregnancies in KSA: distribution according to HPA system.*

Platelet alloantigen	Estimated risk (%)	Total (%)
HPA-1a	0	
HPA-1b	24	24
HPA-2a	3.84	
HPA-2b	4.55	8.39
HPA-3a	4.72	
HPA-3b	15.39	20.11
HPA-4a	1.96	
HPA-4b	3.84	5.8
HPA-5a	2.97	
HPA-5b	20.96	23.13

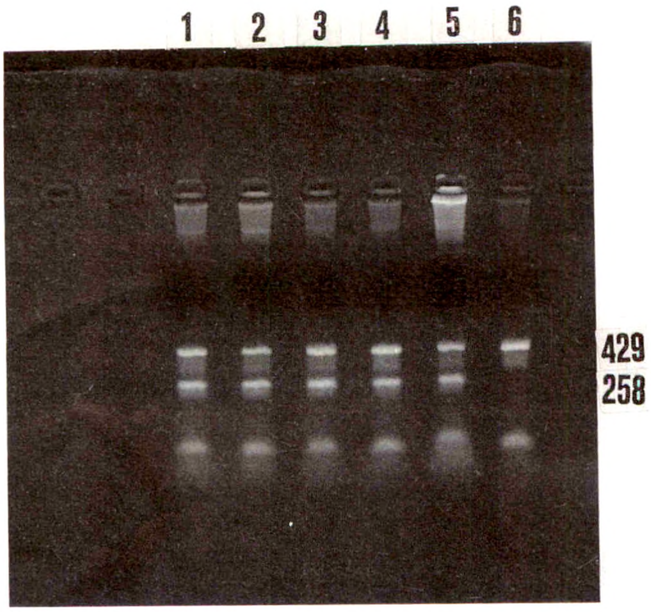

FIGURE 1. Agarose gel electrophoresis of PCR-amplified HPA-2 genes (a & b) from father (1 & 2), son (3 & 4) and mother (5 & 6). Wells 1, 3 & 5 contained HPA-2a specific primer. Wells 2, 4 & 6 contained HPA-2b specific primer. The fast band (258bp) represents the amplified HPA-2 gene. The slow band (429bp) represents the amplified positive control (HGH) gene. The father and son are heterozygous (i.e., have both HPA-2a & 2b). Mother is homozygous for HPA-2a.

The infant's platelets were not available for direct PIFT. Anti-HLA antibodies in the mother's serum were excluded by standard NIH lymphocyte cytotoxicity assay. Organ and non-organ-specific antibodies were tested by indirect immunofluorescence test using a composite block and showed no antibodies in maternal serum.

Platelet Genotyping

Five mL EDTA blood was obtained separately from the baby, the mother and the father, and DNA was isolated from lymphocytes by salting out and ethanol precipitation as previously described.[6]

Isolated DNA was amplified by the PCR-SSP technique described earlier,[7] using a Perkin Elmer thermal cycler (Gene Amp PCR system 9600). The PCR reaction mix (10 µL) contained 2 µL (200 ng) genomic DNA, 1 µL (20 pmol) of common and 1 µL of specific primer (HPA-1a or HPA-1b, etc.), 2 µL of positive-control (sense and antisense) primers for human growth hormone (HGH), 0.2 µL (200 µmoL) of dNTP mix, 1 µL of 10x reaction buffer, 0.09 µL (0.04 U) of taq polymerase, and 2.72 µL double-distilled water. Amplification was carried out for 34 cycles with three different set-ups of decreasing annealing temperature (i.e., 68°C, 61°C and 51°C).

Three primers were used for each HPA system: one common and two specific primers (for a or b). Each tube contained an allele-specific and a common primer. A 50 bp ladder was used as reference for the size of the amplicon. The amplified product was detected by electrophoresis on 2% agarose gel impregnated with ethidium bromide (140 v, 20 minutes).

Results of HPA1-5 genotyping of the family are shown in Table 1. Genotypes of HPA-3, HPA-4 and HPA-5 were the same in all three family members, but there were discrepancies in the distribution of HPA-1b and HPA-2b. It is obvious from Table 1 that the only HPA system that could have contributed to NAIT in this case was HPA-2b. This antigen was absent on the mother's platelets but expressed on both the father's and baby's platelets. Figure 1 shows the electrophoretic pattern of HPA-2 genotyping of the family.

Discussion

Isolated thrombocytopenia in our Saudi neonate was not initially suspected as NAITP, as there was no history of a previously affected sibling. Other etiologies of thrombocytopenia, including DIC, infection, maternal ITP, consumption hemangioma and drug intake were excluded. Diagnosis of NAIT was virtually confirmed by positive indirect PIFT and spontaneous recovery of the thrombocytopenia. However, identification of the specific platelet alloantigen linked to thrombocytopenia in this infant was confirmed by PCR. This was necessary for counselling the family regarding future pregnancies. It was also relevant for the management of future pregnancies, with or without the need for intrauterine treatment or cesarean delivery. Maternal platelets can be collected in advance for later transfusion to the newborn if NAIT is anticipated. Further genotyping becomes essential in those cases where PIFT or other serological tests are negative.

In our patient's family, the father was heterozygous for HPA-2b, whereas the mother was homozygous for HPA-2a allele. This means that there is a 50% chance of having HPA-2b-positive babies in future pregnancies. This may explain the previous three unaffected children, who were probably homozygous for HPA-2a. It is also remotely possible that the two abortions might well have been due to NAIT, as a result of the heterozygous state of the fetus. However, further pregnancies would be carefully monitored for possible recurrence of the same problem.

Among the different platelet alloantigens recently classified by Von dem Borne,[8] the most frequently implicated in Caucasians are HPA-1A (PI^{A1}), accounting for 78%, and HPA-5b (Br), accounting for 19% of cases of NAIT. Thus, HPA-2 (Ko), HPA-3 (Bak) and HPA-4 (Pen) account for only the remaining 3%.[9] The contribution made by various HPA to NAIT appears to be racially determined; the Japanese, for example, have a higher incidence of anti-HPA-4-related NAIT.[7] Anti-HPA-1 is the most commonly reported cause of NAIT. HPA-2 (Ko) system is a rare cause of NAIT. Since the discovery of this system in 1960, only a few cases have been reported. One rare case of prolonged neonatal alloimmune megakaryocytopenia was attributed to anti-HPA-2b. Molecular studies have shown that the two allelic forms of HPA-2 (i.e., 2a and 2b) are polymorphic at a single amino acid at position 145 from the N-terminal elastase-sensitive fragment of glycoprotein 1b chain.[10]

To our knowledge, this is the first reported case of NAIT due to anti-HPA-2b in Saudi Arabia. The HPA system responsible for the majority of NAIT in the Kingdom is not yet known. In our recent study on healthy Saudis, HPA distribution revealed a pattern peculiar to this population that was different from Western and Oriental populations.[11] The distribution of the different HPA alleles in Saudis was as follows: HPA-1a 80%, HPA-1b 20%, HPA-2a 80.5%, HPA-2b 19.5%, HPA-3a 88%, HPA-3b 12%, HPA-4a 97%, HPA-4b 3%, HPA-5a 84.5%, and HPA-5b 15.5%.

The estimated risk (ER) of NAIT in pregnancies can be predicted from the probability that an antigen-negative mother becomes pregnant with an antigen-positive baby. ER for NAIT=aa×(ab+bb)+bb×(ab+aa), where a and b are codominant alleles of each HPA type. The ER for NAIT associated with anti-HPA antibodies is: HPA-1a=0%, HPA-1b=24%, HPA-2a=3.84%, HPA-2b=4.55%, HPA-3a=4.72%, HPA-3b=15.39%, HPA4a=1.96%, HPA-4b=3.84%, HPA-5a=2.97% and HPA-5b=20.96%. It must be stated that not all pregnancies at risk progress to clinical disease. This may be partly due to variable immunogenicity of different HPA. It may also be related to the immune response in the mother (i.e., high or low responder). Some authors have described the influence of HLA-DR phenotype in the mother on her immune response to foreign HPA. Thus mothers with the HLA haplotypes B8, DR3, DRw52 are reportedly more likely to develop anti-HPA antibodies when stimulated.[12]

These estimated risk figures overestimate the actual risk. NAIT is seen much less clinically than is suggested by these figures. This data, however, may be useful to predict the relative contribution of different HPA antigens and antibodies. As can be predicted from Table 2, approximately half of the NAIT in Saudis may be related to anti-HPA-1b and HPA-5b antibodies. This is more or less similar to Western experience. Here again anti-HPA-2b is predicted to play a less significant role (around 5%). Thus, our patient may represent one of those rare cases. The actual contribution of HPA system to NAIT in Saudis requires a larger study.

PCR-SSP is a useful method for the diagnosis of this rare condition, and we hope this method, as well as genetic counselling, will be introduced in other laboratories in the Kingdom.

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MALIGNANT CHYLOTHORAX TREATED BY TALC PLEURODESIS: A CASE REPORT AND REVIEW OF THE LITERATURE

Ahmed H. Banjer, FRCS; Mohammed A. Siddiqui, FRCS;
Mohammed O. Al-Fattani, MRCP; Baker A. Nigme, MD

We report a case of malignant chylothorax due to Burkitt's lymphoma, treated successfully by talc pleurodesis. Various methods of treatment of chylothorax are discussed.

Case Report

A four-year-old non-Saudi boy, a known case of stage III Burkitt's lymphoma who was undergoing a chemotherapy program, presented two months following the diagnosis with severe shortness of breath and repeated cough. He was first seen in the Oncology Clinic as a follow-up visit after the induction of chemotherapy. The parents denied any history of fever or trauma.

Clinical examination revealed marked reduction of air entry, with stony dull percussion note on the right hemithorax. Other systemic examinations were normal. Results of blood investigations revealed the following: WBC 7.1×10^9/L; hemoglobin 11.1 g%; erythrocyte sedimentation rate 5 mm in the first hour; glucose 191 mg/dL; total protein 5.3 mg/dL; and arterial blood gases within normal range. Chest x-ray revealed complete opacification of right hemithorax (Figure 1). Thoracentesis was performed, and it revealed white milky aspirate, analysis of which showed WBC 1.1×10^9/L, with 90% lymphocytes and 10% neutrophils, glucose 181 mg/dL, total protein 8.8 g/dL, cholesterol 376 mg/dL, triglyceride 2980 mg/dL, and amylase 60 U/L. CT scan revealed left hilar and abdominal multiple lymph nodes enlargement, with right pleural effusion and no parenchymal lung disease.

The working diagnosis was malignant chylothorax due to obliteration of lymphatic channel. An intercostal tube was inserted, and 800 mL of aspirate was drained soon after insertion. The patient continued to drain 300-400 mL/day, despite a low-fat and medium-chain triglyceride diet.

As the patient failed to respond to conservative treatment of chlothorax for one week and the amount of tube drainage was not regressing, a decision was made to perform pleurodesis, using talc powder. At surgery, using single lumen endotracheal tube and through muscle-sparing mini-thoracotomy at the fifth intercostal space, 5 g of talc powder was sprayed over the lung and pleural surfaces with powder insufflator (GU medical system, London, UK). There was no identifiable site of chyle leak, only generalized oozing from the pleural surface. The postoperative period was uneventful and the second chest tube was removed on the seventh postoperative day. Serial follow-up chest x-ray, up to one year post-surgery, showed full expansion of the lung with no recurrence of pleural effusion (Figure 2).

Discussion

Chylothorax is one of the differential diagnoses of complete opacification of hemithorax on chest radiography, as seen in our reported case. Other causes include pleural effusion, hemothorax, empyema and lung collapse.[1] Chylothorax is usually found in malignant diseases and following cardiothoracic surgery or blunt trauma of the chest.[2-3] In malignant diseases, such as lung cancer and lymphosarcoma, the thoracic duct can be involved by primary growth direct invasion, lymphatic permeation, or tumor embolization. Marts et al. reported 29 cases of chylothorax, 26 of which were due to surgical trauma.[2] Lymphoma and leukemia are known to be complicated by chylothorax,[4-5] and lymphoma is said to be the most common cause of non-surgical chylothorax.[3]

The diagnosis of chylothorax includes chest radiography, but thoracentesis is the most important diagnostic tool to reveal milky colored aspiration with high levels of triglyceride and chylomicrons. Other methods described in the literature include lymphography of the thoracic duct. Nagan et al. described the role of lymphography in 10 patients with chylothorax following thoracic surgery, to identify the site of leakage and obstruction.[6]

Initial lines of treatment described in the literature include dietary modification with low-fat or medium-chain triglyceride diet, gut rest by giving parenteral nutrition,

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From the Departments of Surgery (Drs. Banjer and Siddiqui), Pediatrics (Dr. Al-Fattani), and Anesthesia (Dr. Nigme), Al-Noor Specialist Hospital, Makkah, Saudi Arabia.

Address reprint requests and correspondence to Dr. Banjer: Thoracic Surgery Unit, Al-Noor Specialist Hospital, P.O. Box 6834, Makkah, Saudi Arabia.

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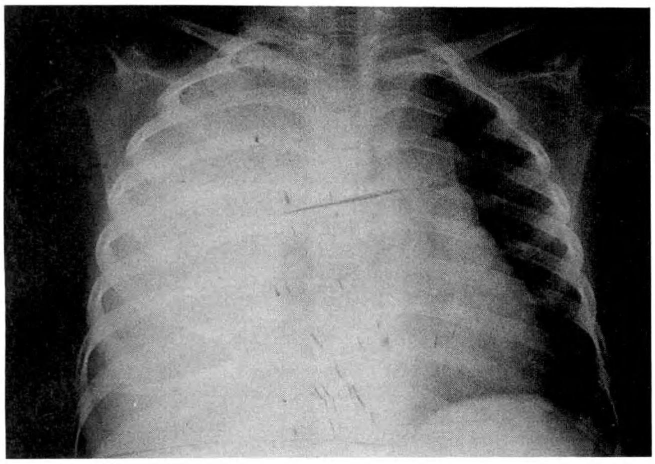

FIGURE 1. PA chest x-ray shows complete opacification of right hemithorax due to chylothorax.

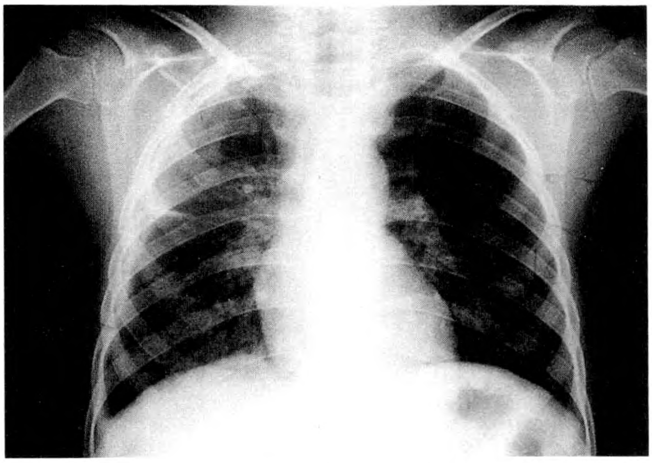

FIGURE 2. One-year postoperative chest radiograph shows complete expansion of right lung without recurrence of chylothorax.

and drainage maintained by tube thoracostomy. Marts et al. showed 79% of the cases with chylothorax resolved by these conservative methods, while only 21% of the cases required surgical ligation of the thoracic duct. Similar results have been described in another report.[7] Other surgical methods include thoracoscopic ligation of thoracic duct,[3] pleuroperitoneal shunt insertion[8] in chylothorax following cardiac and non-cardiac surgery, and primary anastomosis of injured duct.

The most simple and effective method is chemical pleurodesis by talc powder. Talc powder is widely used for the treatment of malignant pleural effusion and pneumothorax.[9] It is a strong sclerosing agent which can be instilled into pleural space through the chest tube or thoracoscopically by insufflation. Weissberg and Ben-Zeev reported their experience of talc pleurodesis in 360 patients, 169 with malignant effusion, and 122 with recurrent spontaneous pneumothorax. Their results were excellent in 84.4% and 86.6%, respectively.[9]

Some surgeons use additional procedures to talc pleurodesis at surgery, such as clipping of thoracic duct and application of fibrin glue,[3] while others perform pleurectomy.[7] In certain cases, decortication is advocated in long-standing chylothorax.[10] The choice between various surgical interventions depends on the primary cause and available resources. Clipping or ligation might be required in traumatic injury of thoracic duct, however, we believe that primary anastomosis, as described by some surgeons, is time consuming and not mandatory. Furthermore, the use of fibrin glue injection intrapleurally or pleuroperitoneal shunting are much more expensive, compared to talc powder insufflation. In this reported case we performed mini-thoracotomy, as the facilities for thoracoscopy for children were not available in our hospital. We believe that instillation of the powder through intrathoracotomy (tube thoracostomy) as practiced by some surgeons, will give localized pleurodesis, and talc powder will not be distributed all over the pleural surfaces.[9] Talc pleurodesis is not expensive and is easily applicable. It does not require formal thoracotomy and is a bloodless intrathoracic procedure, as compared to pleurectomy, and is highly recommended in malignant effusion. It was sufficient to resolve the chylothorax without recurrence even after one year of follow-up, but chemotherapy for lymphoma should not be ignored, as it may play a part in its resolution.

In this reported case, we believe that talc pleurodesis is the main factor of resolution of chylothorax, as documented by early serial post-surgical chest x- rays. Talc powder is available in most of the hospital pharmacies in Saudi Arabia, but it is in an unsterile form. Unfortunately, sterilization facilities are not available in most of the hospitals. Talc powder requires either gamma radiation or prolonged heat sterilization for one hour at 160ºC, which cannot be provided by ordinary hospital autoclaves.[11]

Our source of sterile talc powder was Royal Brompton Hospital's pharmacy in London, U.K. We used only 5 g of purified talc powder in our case, because some workers observed the occurrence of mesothelioma after the use of unpurified talc powder.[12] Purified talc is free of carcinogenic contaminants and suitable for clinical use. Other reported complications are trapping of the lung and adult respiratory distress syndrome (ARDS).[9,13] These complications are probably related to the amount of talc used. According to Rinaldo et al.,[13] ARDS occurred in patients who have used 10 g of talc, but was not observed in patients who received 5 g of talc. Most surgeons advise the use of a minimal amount of talc powder to avoid these complications. The recommended dose range is between 2-5 g of purified powder.[9,14] It is the responsibility of the surgeon to control and decide the amount of the talc powder insufflated into pleural space. The most important factor of the success of pleurodesis is that the powder is sprayed evenly all over the pleural surfaces.

In summary, talc pleurodesis is effective in malignant chylothorax. To our knowledge, this is the first case report in Saudi Arabia illustrating how a simple procedure such as talc pleurodesis can provide relief of dyspnea due to malignant chylothorax as a result of central lymphatic obstruction.

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INTRAVASCULAR LARGE-CELL LYMPHOMA: REPORT OF AN UNUSUAL CASE

Hind Al-Humaidan, MD, FRCPA; M. Ashraf Ali, MD, FRCPC, FCAP; Adnan Ezzat, MB, BCh, FRCPC

Intravascular large cell lymphoma (IVL) is characterized by a massive proliferation of neoplastic mononuclear cells within the lumina of vascular channels. It was originally thought to represent an endothelial neoplasm, however, recent studies have clearly established its lymphoid nature. It usually occurs in the middle-aged or elderly. The clinical course is characterized by unexplained fever, microvascular skin lesions, dementia, neurologic changes, and progressive multisystem failure.[1,2]

A characteristic histopathologic feature of this disorder is the extensive intravascular proliferation of atypical mononuclear cells within the lumens of venules, arterioles, capillaries and small arteries. The lymphoma has a tendency to involve small blood vessels of the skin and central nervous system. Other organs, such as kidneys, heart, spleen, lymph nodes, lungs and endocrine organs, may be involved as well. Various clinical abnormalities have been frequently described in this disease, including low serum levels of albumin, sodium and chloride, high erythrocyte sedimentation rate, disturbance of liver and renal functions and positive rheumatoid factor and antinuclear antibodies. The diagnosis is often made postmortem.[3-5]

The first case of IVL was reported by Pfleger and Tappeiner in 1959.[1] Several cases and small series have since been published. The majority of these cases were diagnosed postmortem. We are reporting a case of IVL which had an unusual clinical course, with absence of skin or CNS symptoms, and which initially had a good response to chemotherapy.

Case Report

A 57-year-old female presented to our hospital in June 1996 with a few months' history of fever and chills lasting for two hours, and then resolving spontaneously. This had later increased in frequency to three attacks per day. The fever was not associated with diaphoresis, arthralgia, body aches, skin rash, chest pain, cough or shortness of breath. On examination, the patient was found to be pale, with muscle tenderness and splenomegaly (2 cm below costal margin). There was no peripheral lymphadenopathy or hepatomegaly.

Investigations revealed a hemoglobin of 82 g/L (normocytic, normochromic), with an ESR of 80 mm/hour. She had raised liver enzymes, ALT 60 units/L (normal 10-50), alkaline phosphatase 22 μ/L (30-125), AST 128 μ/L (10-45), the total bilirubin was 11 (0-21) nmol/L, and albumin 32 g/L (36-48). LDH on admission was 3604 IU (297-537). Ultrasound of the abdomen revealed an enlarged spleen (19 cm), with no focal lesions. The liver showed normal parenchyma and there was no para-aortic lymphadenopathy. CT scan of the abdomen revealed mild hepatomegaly and moderate splenomegaly without focal changes. The density of the liver on non-contrast images was slightly higher than normal. No evidence of lymphadenopathy was noted. Blood cultures were negative and bone marrow and liver biopsy were taken. A bone marrow biopsy revealed a hypercellular marrow with large intravascular, mononuclear cells in the small blood vessels and sinusoids (Figure 1). The liver biopsy showed focal plugging of sinusoids with large lymphoid cells (Figure 2). Immunohistochemical staining on both biopsies revealed that most of the mononuclear cells stained for LCA and L-26 showed no staining with CD3, indicating that the cells were of a B-cell phenotype (Figure 3).

The patient was treated as intermediate/high-grade malignant lymphoma, and started on CHOP (cyclophosphamide, hydroxydaunomycin, Oncovin and prednisone) chemotherapy. CT scan of the head revealed no focal brain lesion and no enhanced abnormality was detected. However, mild generalized brain atrophy was seen with enlarged ventricles. She received six cycles and went into complete remission, as evidenced by the absence of her symptoms, normalization of her liver function tests, and radiological views of her spleen and liver, and negative bone marrow. She was disease-free for four months before her fever recurred, with splenomegaly and positive bone marrow. She was treated intensively with second-line chemotherapy, followed by high-dose chemotherapy at an overseas center. However, her disease

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From the Departments of Pathology and Laboratory Medicine (Drs. Al-Humaidan and Ali) and Oncology (Dr. Ezzat), King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia.

Address reprint requests and correspondence to Dr. Al-Humaidan: Department of Pathology and Laboratory Medicine, MBC-10, King Faisal Specialist Hospital & Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia.

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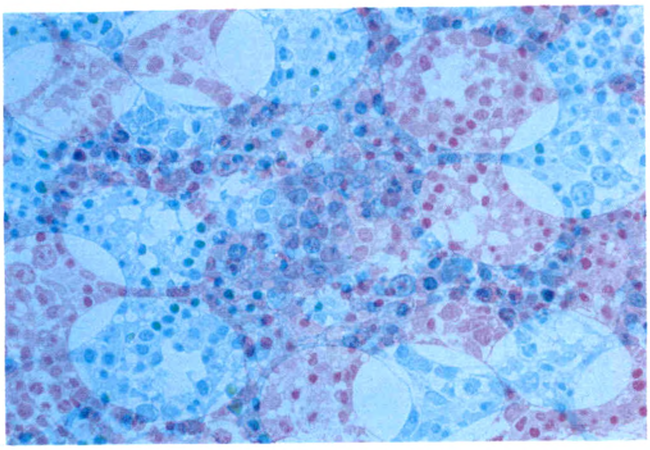

FIGURE 1. Bone marrow biopsy with mononuclear cells in small blood vessels.

persisted and she developed several complications, including septic shock that was fatal.

Discussion

Intravascular (angiotropic) large cell lymphoma is an extensive proliferation of neoplastic mononuclear cells within the lumina of blood vessels. The disease is characterized by involvement of the skin and central nervous system, and disseminates rapidly with involvement of multiple organs. The prognosis is usually extremely poor, with rapid death despite chemotherapy.[1] Most patients present with fever of unknown origin and nonspecific cutaneous and neurologic manifestations. Cutaneous lesions may be confused with mycosis fungoides, sarcoidosis, vascular neoplasms, or cutaneous involvement by lymphoma or leukemia.[5,6] The histogenesis of IVL is still controversial. Benign forms have been described in association with bacterial endocarditis and are distinguished by their clinical and histological features.[3,7]

Originally, these intravascular cells in IVL were thought to be of endothelial origin. This observation was based on the presence of tumor cells attached to the endothelium of involved blood vessels. However, immunohistochemical stains have failed to demonstrate consistent staining for factor-VIII-related antigen, an endothelial cell marker.[3] Ansell et al. and Bhawan et al. were the first to demonstrate that the neoplastic intraluminal cells are of lymphoid origin of B-cell lineage.[8,9] Otrakji et al. demonstrated specific B-cell immunoglobulin gene rearrangement by Southern blot hybridization analysis on deoxyribonucleic acid (DNA) extracted from neoplastic cells present in the adrenal tissue obtained at autopsy from a patient with IVL. This study provided the first genotypic evidence for the monoclonal proliferation of B-cells in this condition. They also demonstrated strong positive reaction with anti-Kappa light chain antibody in cryostat cut fresh frozen section.[7]

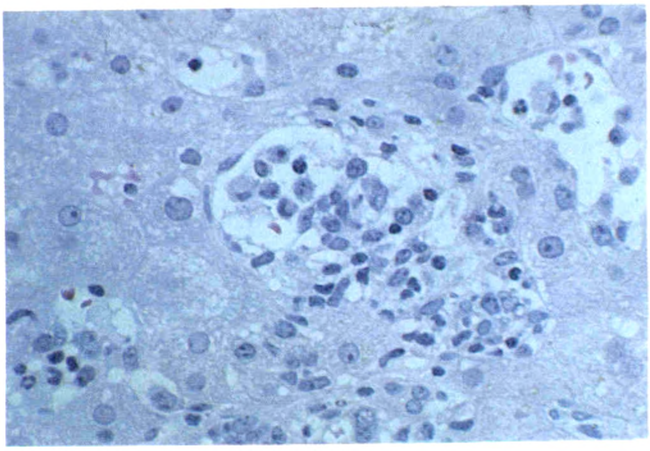

FIGURE 2. Liver biopsy shows plugging of sinusoids in large mononuclear cells.

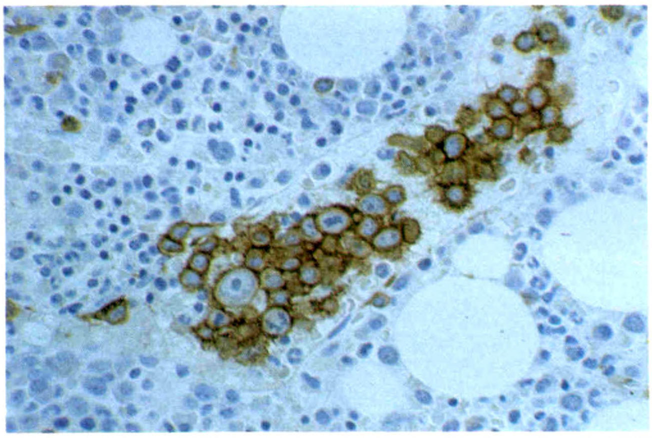

FIGURE 3. Immunohistochemical stain on the mononuclear cells stain for L-26.

Obviously, intravascular lymphomatosis represents an unusual type of lymphoproliferative disease in which many aspects are as yet poorly understood, e.g., site of origin and types of lymphoid cells involved (heterogeneity of the disease). Also misunderstood are the mechanisms that mediate the exclusive affinity of the lymphoma cells to certain types of blood vessels (capillaries, postcapillary venules) and prohibit the colonization of the organs most commonly linked to lymphoma, such as lymph nodes, spleen and bone marrow.[2,10]

Histopathologic diagnosis of IVL on biopsy material is usually problematic, since many pathologists are still not aware of this entity. Most of the reported cases in the literature have been diagnosed at autopsy.[11,12] In our case, bone marrow biopsy was initially interpreted as reactive, however, a liver biopsy revealed atypical large lymphoid cells in the sinusoids, which revealed a B-cell phenotype, suggesting the diagnosis of IVL. A review of bone marrow biopsy showed similar involvement. This is the first case of IVL reported in Saudi Arabia, and we believe that increased awareness of this type of lymphoma will result in recognition of additional cases.

Most of the patients with IVL present with skin and CNS involvement, however, in our case, careful evaluation of the patient failed to reveal dermal and CNS involvement. Our patient had abnormal liver function tests with transaminases and a high level of LDH. She had hypoalbuminemia, hyponatremia, anemia, and elevated ESR. She responded to CHOP chemotherapy and the fever subsided. Among 35 patients reported in the literature who received chemotherapy, 43% attained complete remission. This suggests that IVL is a high-grade, non-Hodgkin's lymphoma and long-term survival may result in patients who are treated with aggressive combination chemotherapy.[13]

In the literature, several synonyms have been used to describe this entity, such as malignant angioendotheliosis, neoplastic angioendotheliosis, malignant angioendotheliomatosis, hemangioendotheliosis, angioendotheliomatosis proliferans and intravascular lymphomatosis. In view of conclusive evidence favoring a lymphoid phenotype of the tumor cells, it is believed that intravascular large cell lymphoma would be a more appropriate name for this disease, since it accurately describes the clinical, histological and biological features seen in this disorder.[2,3]

In summary, it is hoped that this report of an unusual case of IVL which had no CNS or skin involvement and which initially responded well to chemotherapy, will increase awareness among pathologists and oncologists regarding this entity.

Acknowledgements

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Brief Reports

ACUTE LEUKEMIA IN KING FAHAD GENERAL HOSPITAL, JEDDAH

Abdul Rahim Gari-Bai, Fachartz; Badr Ali Arab, MBBS;
Mir Asif Ali Khan, MD

The incidence of leukemia is high in Saudi Arabia.[1-3] The symptomatology of the disease is nonspecific, demanding a high degree of suspicion among general practitioners and physicians who are primary healthcare providers for the population at large. Delay in diagnosis definitely has an adverse effect on the outcome of this potentially curable malignancy.

The management of leukemia requires a specialized setup, with adequate diagnostic and treatment facilities. From our experience in managing acute leukemia, we have noticed that most patients present late, with associated severe infections, simply because the diagnosis had not been made earlier, even though there had been abnormal hematological parameters on routine blood examination. Secondly, some patients insist on referral to a tertiary center, which too often delays initiation of specific management. We therefore decided to undertake a prospective study of all patients with leukemia attending our hospital. This study was designed to address the modes of presentation of the disease, implications on referral procedures, and more importantly, prospects of management of the disease in our hospital.

Patients and Methods

King Fahd Hospital in Jeddah is the largest Ministry of Health hospital in the Western province of Saudi Arabia, with a 1200-bed capacity. It is the main referral hospital in both the Western and Southern regions. All patients in whom the diagnosis of acute leukemia has been confirmed were included in this prospective study, which spanned a two-year period from March 1992 to March 1994. Common clinical problems, i.e., those symptoms which prompted the patients to seek medical help, were identified. The duration of these symptoms and the number of hospitals visited by the patients before the diagnosis was made was also recorded. Diagnoses were made or confirmed in our hospital by standard hematological practice. Classification of leukemia was confirmed using morphological and cytochemical studies. Flow cytometry and cytogenetic studies were not performed, since we do not have the required facilities. However, immunophenotyping was done in three patients who posed difficult diagnostic problems, using flow cytometry elsewhere.

The induction regimen for acute myeloid leukemia (AML) consisted of DAT, as follows: daunorubicin 60 $mg/m^2/d$, iv bolus on days 1-3; cytarabine (ARA-C) 100 $mg/m^2/d$, days 1-7 24-hr infusion; and 6-thioguanine 200 $mg/m^2/d$ in two divided doses orally. The induction regimens for acute lymphoblastic leukemia (ALL) were the German protocols for children[4] and for adults.[5]

Results

Thirty-four patients with acute leukemia were seen in the two-year study period. On average, a patient had been to three medical centers (range 1-6), either private or government hospitals, before being referred to us. The duration of symptoms ranged from 14 to 120 days. The

TABLE 1. *Characteristics, symptomatology and hematology profile of patients.*

Number of patients	34
Saudi/non-Saudi	16/18
Adults/children	28/6
AML/ALL/AL	21/11/2
Treatable/untreatable	21/13
Mean age (range)	36 (2-83)
Symptoms at presentation	
Anemia	27
Febrile illness	17
Bleeding tendency	14
Lymphadenopathy	12
Hepatomegaly	10
Splenomegaly	10
Sepsis	3
Mediastinal mass	2
Gum hypertrophy	2
Hematology profile	
Anemia	31
Thrombocytopenia	30
Anemia and thrombocytopenia	28
Anemia or thrombocytopenia	5
Neither anemia nor thrombocytopenia	1
WBC $<2.5 \times 10^9/L$	4
WBC $2.5\text{-}15\ 10^9/L$	3
WBC $>15 \times 10^9/L$	27

From the Department of Medicine, King Fahad General Hospital, Jeddah, Saudi Arabia.

Address reprint requests and correspondence to Dr. Gari-Bai: Department of Medicine, King Fahd General Hospital, P.O. Box 10744, Jeddah 21443, Saudi Arabia.

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most common clinical problem upon presentation was febrile illness (14/34). Three patients had symptoms of anemia and eight had hemorrhagic diathesis as their main clinical problem. Table 1 shows the patient characteristics, the symptoms and hematological profile at the time of presentation. Four non-Saudi patients opted to seek treatment in their native countries. Eleven patients were not considered for intensive treatment. Of these, five had severe infection, four were elderly, one patient was in coma, probably due to cerebral leukostasis, and another had AML-M3 with disseminated intravascular coagulation (DIC).

Nineteen patients were considered for induction chemotherapy. Of these, five demanded referrals to a tertiary center, which were promptly granted, but two of these patients died pending their acceptance.

Induction chemotherapy was started in fourteen patients. One of the patients left against medical advice and induction therapy failed in another with AML-M3 subtype. The remaining 12 patients (6 ALL and 6 AML) completed a planned induction phase of treatment.

Discussion

The spectrum of clinical presentation of our patients with acute leukemia is similar to well-known data in the literature.[6,7] Although most of our patients had anemia, they probably adapted to it and presented with febrile illness or other complications. As is shown in the study, most of the patients were seen at various hospitals before a definitive diagnosis was made, even though the patients had abnormal hematological parameters. The significance of blood smear examination in demonstrating blasts, which was diagnostic in all our patients, cannot be overemphasized, as has been shown in detecting relapses in AML.[8] It was because of a delay in diagnosis that 18% (6/34) of patients were not considered for treatment. The patients had serious associated infections, which are a common cause of death among leukemic patients.[9]

Undoubtedly, tertiary centers in Saudi Arabia alone cannot take up the management of all acute leukemia cases because of the high prevalence of the disease and limited bed capacity. Referral from regional hospitals is associated with delays in initiating specific management, which has an adverse effect on a rapidly growing malignancy, such as acute leukemia. We lost two patients who refused to have treatment under our care and who were waiting for a reply from a tertiary center.

To address the issue of prospects of treatment of acute leukemia in our hospital, where certain facilities such as isolation rooms and proper blood bank support are lacking, we defined successful treatment as completion of one induction course for AML, and four weeks of the protocol for ALL. This initial period of treatment is obviously the most demanding phase of treatment. Twelve of the thirteen patients completed this initial induction successfully. This correlates well with general clinical experience.

From this study, which probably reflects the prevailing situation in the management of leukemia in most of the regional hospitals in Saudi Arabia, we conclude that there is a need to increase awareness of the early stage of leukemia among local practitioners. We also recommend that facilities in regional hospitals should be improved and updated, so that patients can be induced into remissions, and when indicated, can later be referred for bone marrow transplant at a tertiary center, such as King Faisal Specialist Hospital and Research Centre in Riyadh. This would ease the burden on the tertiary centers and avoid delays in initiating specific management of this potentially curable malignancy without compromising the overall results.

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THE PATTERN OF SKIN DISEASES IN HAIL REGION, SAUDI ARABIA

Anchala Parthasaradhi, MD; Ali Faheid Al Gufai, MD

The prevalence of skin diseases in any community depends upon various factors, namely the genetic and racial constitution, the social and hygienic standards, customs and occupations, the nutritional status and age structure of the community, climatic factors, state of industrialization, etc. In addition, the diagnostic competence of doctors, special interest and expertise of dermatologists, the availability of expert diagnostic facilities and new methods of therapy contribute to the higher incidence of certain skin diseases in a particular country or community.[1]

The literature concerning the patterns of both general and specific skin diseases is rather scanty, and only a few published reports are available from the Kingdom. Though community-based studies are the best to determine the incidence of a particular disease, they are difficult to carry out. As such, most of the studies to determine the incidence or prevalence of the dermatological diseases are based upon hospital attendance. The present study, aimed at analyzing the pattern of various dermatoses, was carried out over a two-year period from July 1995 to June 1997 at the Dermatology Unit of King Khalid Hospital (KKH), Hail, and was based on the hospital attendance of the patients.

Patients and Methods

A register of all the new patients seen by the Specialists in the Dermatology Unit of KKH over the two-year period was maintained, and the age, sex, nationality and the diagnosis of each patient recorded. Clinical diagnoses made by the dermatologists were corroborated with skin biopsies and other laboratory reports wherever necessary, and the diseases were classified into different groups in accordance with the International Classification of Diseases (ICD-9, 1975). The data thus obtained from the records was compared with studies from other parts of the world and from other regions of Saudi Arabia.

TABLE 1. *Various common dermatoses seen at King Khalid Hospital, Hail, from July 1995-June 1997.*

Disease group (ICD-9) in order of frequency	# of cases (%)
Eczemas (ICD 690-692)	538 (16.31)
Viral infections (ICD 051.2, 052-054, 078, 078.1)	422 (12.8)
Acne and related conditions (ICD 706, 695.3)	410 (12.43)
Parasitic diseases (ICD 085.2, 132.0, 133.0)	242 (7.34)
Alopecias and related conditions (ICD 704)	242 (7.34)
Pigmentary disorders (ICD 709)	233 (7.06)
Superficial mycoses (ICD 110-112)	205 (6.22)
Papulosquamous disorders (ICD 696.1, 696.3, 697.0)	204 (6.18)
Pyodermas (ICD 680, 682, 684)	91 (2.76)
Prurigo and related conditions (ICD 698)	90 (2.73)
Urticaria (ICD 708)	74 (2.24)
STDs, impotence and infertility (ICD 097.1, 098, 099, 099.4, 054.1, 078, 132.2, 302.7, 606)	55 (1.67)
Drug rash	35 (1.06)
Miscellaneous	457 (13.86)

Results

The different skin diseases seen at King Khalid Hospital, Hail, were classified into 14 groups in order of their frequency of occurrence, as shown in Table 1. A total of 3389 dermatoses were diagnosed in 3298 patients seen over the two-year study period. Saudi nationals comprised 84.05% of the patients and non-Saudis 15.95%. There were 2535 adults above 13 years, and 763 children below 13 years. The male to female ratio was 1.23:1.

Overall, 13 groups of diseases accounted for 86% of all the dermatoses, and when these groups of diseases were analyzed according to age, sex and frequency of occurrence (Table 2), eczema topped the list (16.31%), followed by viral infections (12.80%), acne (12.43%), parasitic diseases (7.34%), alopecias (7.34%), pigmentary disorders (7.06%), and others. Noninfective dermatoses, namely eczema, acne, alopecia, pigmentary disorders and papulosquamous disorders, accounted for nearly 50% of all the dermatoses, whereas dermatoses primarily due to infective etiology (viral, bacterial, fungal and parasitic), accounted for nearly 30% of all the skin diseases. Five groups of diseases (acne, eczema, alopecias, pigmentary disorders, viral infections) accounted for 50% of the female and 38% of male attendance to the clinic. Eczema, viral

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From the Department of Internal Medicine, Dermatology Section, King Khalid Hospital, Hail, Saudi Arabia.

Address reprint requests and correspondence to Dr. Parthasaradhi: Consultant Dermatologist, Medwin Hospitals, Chirag Ali Lane, Hyderabad 500 001, Andra Pradesh, India.

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infections, parasitic diseases, and fungal infections accounted for 62% of all the dermatoses seen in children. Viral warts, alopecia areata, vitiligo psoriasis, superficial mycoses and pyodermas were more prevalent in male patients compared to females.

In the eczema/dermatitis group, atopic eczema was the most common (50.56%), and children accounted for almost 60% of the total number of cases. Contact dermatitis was seen more frequently in adults. Among the infective dermatoses group, primary pyogenic infections (2.76%) were the least common, with viral infections (12.80%) being the most common. Viral warts accounted for 65.64% of the viral infections, followed by herpes zoster (14.93%) and chickenpox (12.80%). All three of these viral infections were seen more commonly in male than in female adults. Herpes zoster was recorded in an 80-year-old male and also in a two-year-old boy. We recorded four cases of orf (ecthyma contagiosum) in Saudi patients (3 male and 1 female), all of whom were engaged in sheep rearing.

Superficial mycosis constituted 6.22% of all dermatoses, and tinea capitis and candidial intertrigo were the most common mycosis seen in children. Cutaneous leishmaniasis was the most common parasitic disease, accounting for 82.4% of cases in children. It also constituted 6.58% of all skin diseases, and was more commonly seen in Saudi children and in non-Saudi adult males. Cases of scabies were seen mainly in expatriate Asians and Egyptians. Vitiligo and melasma accounted for 90% of the pigmentary disorders, and alopecia areata accounted for 52.48% of all the alopecic disorders. Vitiligo and alopecia areata were more common in Saudi males, whereas melasma and diffuse thinning of hair were more prevalent in Saudi females. Psoriasis was the most common papulosquamous disorder, accounting for 57.35% of the cases in that group, followed by pityriasis rosea (24%), which was three times more common in females than in males. Prurigo, urticaria and drug rash, which together accounted for 6% of all the dermatoses, were seen more commonly in young adults. Only 27 cases of sexually transmitted diseases (0.82%) were recorded and gonococcal urethritis (7 cases) was the most common, followed by non-gonococcal urethritis, *Phthirus pubis*, genital warts (four cases each), genital herpes, molluscum contagiosum (two cases each), three cases of TPHA- and VDRL-positivity (test for syphilis) in significant titers without any clinical evidence of syphilis, and one case of chancroid (Bangladeshi male). All these patients tested negative for HIV serology. Bullous disorders, which were included in the miscellaneous group, were relatively uncommon (0.24%), and only four cases of epidermolysis bullosa (simplex, dystrophicus and junctional types), two cases of herpes gestationis, one case each of bullous pemphigoid and subcorneal pustular dermatosis (all Saudi patients), were recorded during the study period. Similarly, among the connective tissue diseases there were 10 cases of discoid lupus erythematosus (8 Saudis and 2 non-Saudi), two cases of systemic lupus, and one case each of systemic scleroderma, morphea and dermatomyositis. A single case

TABLE 2. *Hospital attendance for some common dermatoses at King Khalid Hospital, Hail, according to age, sex, and frequency of occurrence.*

Disease groups	Adults (M/F)	Children M/ F	Total #	% in group	% of total cases
Eczemas					
Atopic dermatitis	60/53	108/51	272	50.56	8.25
Contact dermatitis	81/101	11/7	200	37.17	6.06
Seborrheic and related	22/11	6/1	40	7.44	1.21
Other	14/7	3/2	26	4.83	0.79
Total	177/172	128/61	538	100	16.31
Viral infections					
Warts	127/66	50/34	277	65.64	8.4
Herpes zoster	38/13	5/7	63	14.93	1.91
Chickenpox	37/11	2/4	54	12.8	1.64
Herpes simplex	2/5	3/3	13	3.08	0.39
Molluscum bodies	3/1	3/4	11	2.6	0.33
Orf	3/1	0/0	4	0.95	0.12
Total	210/97	63/52	422	100	12.8
Acne and related					
Acne vulgaris	152/245	3/4	404	98.54	12.25
Rosacea	1/5	0/0	6	1.46	0.18
Total	153/250	3/4	410	100	12.43
Parasitic diseases					
Cutaneous leishmaniasis	105/23	51/38	217	89.67	6.58
Scabies	2/2	5/9	18	7.44	0.55
P. capitis	0/2	0/5	7	2.89	0.21
Total	107/27	56/52	242	100	7.34
Alopecia and related					
Alopecia areata	66/28	16/17	127	52.48	3.85
Diffuse thinning of hair	3/90	0/2	95	39.26	2.88
Other	12/6	0/2	2	8.26	0.61
Total	81/124	16/21	242	100	7.34
Pigmentary disorders					
Vitiligo	58/37	22/19	136	58.37	3.85
Melasma	10/65	0/0	75	32.19	2.88
Other	6/13	3/0	22	9.44	0.67
Total	74/115	25/19	233	100	7.06
Superficial mycosis					
Dermatophytes	39/24	20/13	96	46.83	2.91
Tinea versicolor	30/17	0/0	47	22.93	1.43
Candidiasis	2/20	17/13	62	30.24	1.88
Other	81/61	37/26	205	100	6.22
Papulosquamous disorders					
Psoriasis	59/35	14/9	117	57.35	3.55
Lichen planus	16/18	1/3	38	18.63	1.15
Pityriasis rosea	9/24	4/12	49	24.0	1.49
Total	84/77	19/24	204	100	6.18
Pyodermas					
Furuncles	18/5	2/1	26	28.57	0.79
Impetigo	0/0	9/5	14	15.39	0.42
Folliculitis and others	30/14	5/2	51	56.04	1.55
Total	48/19	16/8	91	100	2.76
STD and others					
Sexually transmitted diseases	24/3	0/0	27	49.09	0.82
Impotence, infertility, etc.	28/0	0/0	28	50.91	0.85
Total	52/3	0/0	55	100	1.67

TABLE 3. *Comparative prevalence (%) of a few common skin diseases in different countries.*

Disease groups	Calcutta	Kenya	Leeds	Abu Dhabi	Hail
Eczemas	15-20	28.1	22.7	20.98	16.31
Pyodermas	30-40	6.4	1.1	2.55	2.76
Superficial mycoses	15-20	9.5	3	5.47	6.22
Viral warts	2	2	19.5	5.47	8.4
Acne	3.5	3.9	13.8*	9.07	12.25
Vitiligo	4	2.9	NR	3.18	4.12
Psoriasis	0.5-1.5	3.2	4.8	4.49	3.55
Lichen planus	0.5-1.5	1.6	0.8	0.95	1.15

*Special study center; NR=not recorded.

TABLE 4. *Pattern of certain common skin diseases (%) in different parts of Saudi Arabia.*

Disease groups	Al-Jouf[3]	Asir Region[2]	Hail Region
Atopic eczema	14.27	13.77	8.25
Contact dermatitis	9.57	5.99	6.06
Viral infections	8.27	10.12	12.8
Superficial mycoses	7.81	6.15	6.22
Primary pyodermas	7.3	3.19	2.76
Papulosquamous disorders	7.47	4.82	6.18
Alopecia and related	3.98	6	7.34
Acne	9.57	5.45	12.25
Cutaneous leishmaniasis	NA	1.87	6.58
Urticaria	4.95	5.91	2.24

NA=not available.

of squamous cell carcinoma and two cases of basal cell carcinoma—all in Saudi patients and proved histologically—were the only skin malignancies recorded in our study.

Discussion

The city of Hail lies in the northern region of Saudi Arabia and has a pleasant climate. King Khalid Hospital (KKH) is one of the two regional referral hospitals in the city. There are three dermatologists, two of them working at KKH and the other working at Hail General Hospital. As this study was limited to KKH, Hail, it may not entirely reflect the true prevalence of skin diseases in this region, but because of the larger number of patients and longer period of study involved, it probably provides a rough index to what can be found in this area.

When the present study is compared with data available from other countries[5-7] (Table 3), the striking feature is that the eczema group dominated the list (except for Calcutta, India), irrespective of geographical location or climatic conditions, and pyogenic infections showed up far less in Abu Dhabi, Saudi Arabia and Leeds (U.K), reflecting better socioeconomic conditions in these countries. Superficial mycosis constituted 6.22% of all dermatoses in our study, compared to 15%-20% in Calcutta and 9.5% in Kenya, and a low of 3% in Leeds. The high incidence of pyogenic and fungal infections recorded at Calcutta and in Kenya could be due to the poor socioeconomic status (and overcrowding) prevailing in these areas. However, the wide variations seen while comparing the data with these countries could also be due to the fact that some of these studies were done at much earlier periods (late 1960s and early 1970s) when compared to the studies at Leeds (1980-82), Abu Dhabi (1991) and Hail (1995-97).

Acne showed a higher prevalence rate in our study (12.80%), similar to that of Abu Dhabi (9.07%) and Leeds (13.8%), and this may be to due to an increased health consciousness in these affluent societies, where minor disorders are increasingly getting reported, and there is easy access to medical services. Similarly, viral warts showed up much more in Abu Dhabi, Saudi Arabia and Leeds, probably reflecting the sophistication of the community, where a minor disability becomes significant. Vitiligo had similar prevalence rates in Calcutta and Hail (4% and 4.12%, respectively), whereas psoriasis and lichen planus occurred more or less in similar frequencies in Leeds, Abu Dhabi and Hail. It is interesting to note that our findings were similar to the pattern of skin diseases seen in Abu Dhabi, the neighboring Gulf state.

The low prevalence of venereal diseases recorded in our study may not reflect the true prevalence, as most patients with sexually transmitted diseases prefer to go to private practitioners. As well, tracing such patients is difficult as they generally hide the facts of the disease, but does reflect the general trend seen in other industrialized countries, where gonococcal and non-gonococcal urethritis, genital warts and genital herpes lesions predominate. We did not record any HIV-positive case, which is in accordance with the low prevalence of reported HIV infection in the Kingdom.

On comparing the data obtained from the present study with other studies from within the Kingdom (Table 4), Hail region showed a low prevalence of atopic eczema (8.25%), when compared to a high of 14.27% in Al-Jouf and 13.77% in Asir region. Hail and Asir region recorded similar prevalence rates for contact dermatitis, superficial mycosis and primary pyoderma. Pigmentary disorders, alopecias, acne and viral infections showed higher prevalence rates in Hail region, probably because of the availability of an active female dermatologist, as well as topical and systemic medications in the hospital. The prevalence of papulosquamous disorders was higher in Al-Jouf (7.47%) and Hail (6.18%) when compared to Asir (4.82%) region. Urticaria was more commonly seen in Al-Jouf (4.95%) and Asir regions (5.91%) when compared to Hail (2.24%) region. Hail is one of the known endemic areas for cutaneous leishmaniasis and has a higher incidence (6.58%) of this disease (6.58%) than the Asir region (1.87%).

With increasing affluence, well-organized medical services, rapid industrialization and new methods of therapy, the pattern of skin diseases is changing in many regions of the world, and well-conducted studies could contribute greatly to our knowledge of many skin diseases.

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PROFILE OF CHRONIC HEADACHE PATIENTS IN THE ASIR REGION: A THREE-YEAR STUDY IN ASIR CENTRAL HOSPITAL, ABHA

Ade C. Longe, FRCPC

Headache is one of the most common symptoms encountered in general medical practice, accounting for about 4% of outpatient physician visits.[1] According to different population-based studies, over 70% of the general population experience at least one headache per year,[2] and about 15% consult a physician about this.[3] Headache syndromes were the most prevalent neurological problem encountered in the Thugbah community survey of neurological disorders in the Eastern Province of the Saudi Arabia.[4]

The organization of health care systems and availability of resources in various communities influence clinical practice. Knowledge of the profile of headache patients in specific communities, therefore, facilitates rational utilization of health care resources in the investigation and long-term management of these cases. Most patients evaluated in the Neurology clinic of Asir Central Hospital (ACH), Abha, are referred by general practitioners, often from Primary Health Care Centers. This study was conducted in ACH to define the profile of patients referred to the Neurology clinic for chronic isolated headache, with a view to formulating a management strategy for this common condition.

Patients and Methods

Patients seen specifically for headaches in the Adult Neurology Clinic of ACH, Abha, were prospectively enrolled in the study over a three-year period, beginning April 1995. Chronic headache was defined as one afflicting a patient for a minimum of two weeks. Inclusion criteria were that a patient had suffered chronic headaches and the referring physician had reported the neurological examination as normal. Non-Saudi patients were excluded. A detailed physical examination, including blood pressure measurement and fundoscopy, was performed. Relevant laboratory tests were requested, as indicated by clinical findings. Erythrocyte sedimentation rate was estimated in all patients aged 45 years or more. Although neuroimaging was not a requirement for inclusion in the study, all but nine patients had cranial computed tomography (CT) scans, mainly because they could not be reassured that a serious intracranial lesion was not responsible for their illness. One patient who had typical symptoms of polymyalgia rheumatica had temporal artery biopsy performed.

Headache was classified according to the International Headache Society Classification (1988).[5] Headaches symptomatic of organic or structural disorder are referred to as secondary headaches, while dysfunctional headaches such as migraine and tension-type headache (TTH) are described as primary headaches. Follow-up was conducted in ACH for as long as required to reach a diagnosis and formulate a treatment plan.

The proportions of migraine and TTH headache patients with various clinical features were compared using chi-squared test.

Results

Ninety Saudi patients, constituting 89% of the 101 headache patients of all nationalities seen during the study period, are analyzed in this report. The median age of the patients was 31 years, and the range 11 to 75 years. Sixty-eight patients (76%) were aged 20 to 49 years, while only four were 60 years or older. There were 64 females, resulting in a male to female ratio of 1:2.5.

The headache diagnosis in all patients is shown in Table 1. Primary headache was diagnosed in 79 cases (88%). Eleven patients had headaches symptomatic of a secondary disorder. A 75-year-old female, the eldest in the series, with bifocal meningiomas in the left supratentorial space, had experienced persistent left hemicranial headaches for 13 years. The other brain tumor patient was a 20-year-old female who had a pituitary tumor with suprasellar extension, and had gross clinical features of acromegaly with unilaterally impaired visual acuity. Neither of these patients had papilloedema. Hydrocephalus involving the ventricular system proximal to the aqueduct of Sylvius was diagnosed on brain CT scan in a 20-year-old female with papilloedema who had suffered daily

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From the Department of Medicine, College of Medicine, King Saud University, Abha Branch, Abha, Saudi Arabia.

Address reprint requests and correspondence to Dr. Longe: College of Medicine, King Saud University, Abha Branch, P.O. Box 641, Abha, Saudi Arabia.

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attacks of pulsatile bitemporal and occipital headaches of 12 to 15 hours' duration for two years. Polymyalgia rheumatica was satisfactorily treated with prednisolone 5 mg daily in a 50-year-old female whose temporal artery biopsy was normal, but who had an erythrocyte sedimentation rate of 75 mm in the first hour (Westergren) upon presentation. Headache of increasing severity in the week after spinal anesthesia brought the patient with lymphocytic (aseptic) meningitis and long-standing episodic TTH headache to the clinic.

A comparison of migraine and TTH patients is shown in Table 2. The main differences between these groups were that migraineurs had a higher female to male ratio, onset of headache before 30 years of age in a significantly higher proportion (P=0.03), and experienced headache for more than two years significantly more often (P=0.005) than TTH patients. The duration of symptoms was less than a year in 10 TTH patients and in only one migraineur.

TABLE 1. *Headache diagnosis in 90 Saudi patients.*

Diagnosis	Number of patients
Migraine and variants	39 (43.3%)
Tension-type headache	34 (37.8%)
Mixed migraine and tension-type headache	6 (6.7%)
Brain tumor	2 (2.2%)
Pseudotumor cerebri	2 (2.2%)
Post-traumatic	2 (2.2%)
Hydrocephalus	1 (1.1%)
Polymyalgia rheumatica	1 (1.1%)
Severe hypertension	1 (1.1%)
Tension headache and lymphocytic meningitis	1 (1.1%)
Hypertension and tension-type headache	1 (1.1%)
Total	90

TABLE 2. *Comparison of migraine and tension-type headache patients.*

Characteristics	Migraine N=39	Tension-type headache N=34
Gender ratio (m:f)	1:3.9	1:2.4
Age range (yr)	11-70	17-65
Age at onset (yr)	7-44	12-60
Onset below 30 years of age (no./%)*	25 (69)	14 (44)
Headache duration (range in years)	1-35	1-30
Headache duration <2 yr (no./%)**	13 (37)	21 (72)

*Data missing for 3 migraine and 2 tension-type headache patients; **data missing for 4 migraine and 5 tension-type headache patients.

Discussion

Primary headache disorder was diagnosed in the vast majority of patients referred to ACH for the management of chronic isolated headache. This finding and the preponderance of females patients are similar to previous reports.[6] TTH headache has a higher prevalence (78%) than migraine (28%) in population-based studies.[7] The slightly higher case frequency of migraine compared to TTH in this series may be explained by the selection bias inherent in referred hospital patients.[8] Since migraine is associated with more intense headache than TTH, and by definition interferes with daily activities while TTH does not,[5] migraineurs would be more frequently referred to a neurological service than TTH patients.

The median age and range of our migraine patients was similar to that of TTH cases. However, age of onset of headache was over 30 years in most TTH patients, and they had been symptomatic for a shorter period (<2 years), compared to migraineurs. The former observation is consistent with the reported peak incidence of migraine in the second and third decades.[9] The shorter duration of headache disorder in TTH patients compared with migraine was unexpected, because milder symptom intensity would be expected to delay requests for medical attention. The stresses of life events with increasing age may be factors in the pathogenesis of TTH.[10] Merikangas et al.,[11] however, found no evidence of associated anxiety or depression in TTH patients. Our observation therefore requires confirmation.

Four cases (4%), one of acromegaly, two of pseudotumor cerebri and one of probable aqueductal stenosis, were identified by clinical evaluation as requiring neuroimaging. One brain tumor diagnosis would have been missed without a CT brain scan. This patient's age and persistent unilateral headache were definite indications to search for an intracranial lesion. Cranial CT scan as a secondary screening test for four of our cases (4%), aged 60 years or more, was considered reasonable clinical practice. Intracranial meningiomas and pituitary tumors are often diagnosed incidentally on neuroimaging or at necropsy.[12-14] Other abnormalities of intracranial anatomy, such as arachnoid and poroencephalic cysts, or thin films of hygromas in the elderly, may result in unnecessary neurosurgical consultation.[15] It is prudent to consider the contribution of these lesions to the pathogenesis of a patient's symptoms in specific cases.[16] Indeed, the International Classification of Headaches recognizes an earlier primary headache diagnosis if the characteristics of a patient's symptoms change or new clinical features of an intracranial lesion occur.[5]

Neuroimaging in the investigation of chronic isolated headache is controversial. Based on cost-effectiveness studies, routine neuroimaging for chronic isolated headache is unnecessary.[16,17] The yield from neuroimaging, though low, is not zero.[18,19] The dilemma is that many headache patients, even in the United Kingdom, which operates a family physician system, remain unassured after neurological consultation, and some may request further investigations.[20] In a health care system equipped to provide superior follow-up care, patients might accept reassurance reluctantly while neuroimaging is deferred until a change in their clinical condition warrants it.[15,19] Chronic headache which has not changed in character may, however, be associated with brain tumor.[21,22] Where neurological expertise is in short supply and follow-up is uncertain, the cost and inconvenience of repeated visits to clinics far removed from patients in the hope of a "cure" for chronic isolated headache, the economic cost of lost time and reduced effectiveness of performance at work,[23] and the anxiety engendered by a perceived potentially life-threatening ailment, may influence the need for earlier neuroimaging in the investigation of the headache patient. Probably reassured that an ominous condition was not the cause of their chronic headache, 18 (20%) of our patients did not return to the clinic for follow-up after cranial CT scans that were normal.

In conclusion, this study documents the profile of headache patients referred to ACH, Abha. Although most patients suffered from a primary headache condition requiring only clinical evaluation, cranial CT scan was often performed to reassure patients of the absence of an ominous structural intracranial lesion.

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Letters to the Editor

Pattern of Referrals from a General Hospital to a Regional Tertiary Health Institution: Samtah Experience

To the Editor: The Kingdom of Saudi Arabia has achieved a remarkable growth in the health sector in the last two decades. The health care delivery system is based on a structured hierarchy comprising primary, secondary and tertiary health institutions. Each of these institutions has facilities and relatively defined responsibilities beyond which there is usually a need for referral to a higher center.[1] Reports on the pattern of referrals from one health institution to the other are scanty. Data obtained from such analysis is useful for health care planning and for maximization of benefits from existing facilities.

We reviewed the records of 1000 consecutive inpatients referred from Samtah General Hospital (SGH) to King Fahd Central Hospital (KFCH), Gizan region's tertiary health institution, during the period 1993 to 1995. SGH is a 100-bed modern hospital and serves a population of approximately 174,000 people.

During the study period, there were 21,889 admissions. The 1000 referrals constituted only 4.6% of these admissions. About 87% of these referrals were from the departments of Medicine, General Surgery, Orthopedics and Pediatrics. The department of Obstetrics and Gynecology contributed only 1.2%. The most common disease groups referred were injury and poisoning (38.2%), diseases of the circulatory system (20.0%), the genitourinary system (8.9%), digestive system (7.3%), the nervous system (6.3%) and neoplasms (5.6%).

In the injury and poisoning group, proximal femoral fractures, head injury, and burns were the most common (29.3%). Among circulatory disorders, acute myocardial infarction and cerebrovascular diseases were the most frequent reasons for referral (17.5%). End-stage renal disease (ESRD) was the most common genitourinary problem referred (6.1%), while upper gastrointestinal (UGI) hemorrhage and gallbladder disease (GBD) were the most frequent digestive disorders (4.8%). The most common neoplasm referred was hepatocellular carcinoma (1.3%) (Table 1).

TABLE 1. *Major indications for referrals (1000 cases).*

Diagnosis	ICD-10	No.
Proximal femoral fractures	S72.1 and 72.2	124
Head injuries	S00 - S09	122
Acute myocardial infarction	I21	95
Cerebrovascular accident	I60-69	80
End-stage renal disease	N18.0	61
Burns	T20-25	47
UGI hemorrhage	K92.0-92.2	29
Gallbladder disease	K80 and 82	19
Hepatocellular carcinoma	C22.0	13

ICD-10=10th Revision of the International Classification of Diseases.

Fewer than 5% of the patients admitted to SGH during the period under review were referred to KFCH for further investigations or management. This represents a low referral rate, and is probably a reflection of the optimal utilization of facilities in the hospital. Despite this, it was necessary for some departments to refer cases which could not be fully investigated or treated due to lack of appropriate facilities. This was especially evident in the management of patients with head injuries, cerebrovascular accidents (CVA), proximal femoral fractures, myocardial infarction, upper gastrointestinal hemorrhage and burns.

Head injuries are very common in our practice. In this series, a considerable number of patients (12.2%) referred to KFCH were for head injuries that required CT scan, a facility that is not available in our hospital. A further need for referral of patients for CT scan in our study was for CVAs (8%). When added to those sent because of head injuries, CT scan was the most common indication for referral (20.2%).

A considerable number of the older population present with proximal femoral fractures because of senile and postmenopausal osteoporosis.[2] Rigid internal fixation, followed by early mobilization, which is now the treatment of choice for most of these fractures, requires image intensification. As this is not available in our hospital, this group of patients were all referred to KFCH. Acute myocardial infarction was the third most common indication for referral (9.5%). All were patients judged suitable for thrombolytic therapy, which is not available at SGH. Thrombolysis is most beneficial in the first six hours after infarction.[3] Institution of this therapy in SGH, which is one hour's travel time away from KFCH, would increase the chances of patients' survival and reduce the referral rate to KFCH.

Chronic hepatitis B and C virus infections and their sequelae are highly prevalent in Gizan.[4,5] In most of our patients with UGI bleeding, the cause is esophageal varices. Occasionally, it is due to a bleeding duodenal ulcer (DU). Since our endoscopy service is not equipped for therapeutic intervention, these patients are often referred to KFCH after the initial resuscitative measures. Upgrading our endoscopy service will no doubt enable us to provide prompt and definitive treatment to such patients.

Burns of less than 20% of body surface can be safely managed in the surgical wards of general hospitals. However, when the head, face, or perineum or more than

20% of the body surface is involved, better results are obtained if the patients are managed in a specialized burn unit. The establishment of such a unit allows for a concentration of facilities and optimal timing of any desired surgical intervention. The 47 cases referred in our series (4.7%) were those with more than 20% burns who were considered to have a reasonable chance of functional as well as cosmetic recovery if treated in a specialized burn unit.

Most of the ESRD patients who were referred to KFCH were done so for the creation or revision of arteriovenous fistulae, as we did not have a vascular surgeon during part of the period reviewed. Occasionally, the attitudes and preferences of patients or their relatives may influence referral to a tertiary health institutions. For instance, while facilities may be available in the general hospitals for open cholecystectomy, patients may prefer to have laparoscopic cholecystectomy in the tertiary centers. A further factor is the awareness of the existence of highly specialized medical facilities in the tertiary institutions at no cost to the patients. This may lead to unnecessary demands for referrals to such institutions when the existing facilities in the general hospitals may be adequate.[6] It is hoped that with better communication from health providers, such demands will be reduced.

It is essential that the highly specialized services offered at the tertiary level hospitals are not overburdened by undeserving referrals. While our referral rate in the period reviewed was reasonably low, we feel that further reductions can be achieved by the provision of a CT scanner, an image intensifier, facilities for thrombolysis, and a fully equipped endoscopy unit in our hospital. Additional benefits that may accrue from this will be the savings on transport and manpower required for the transfers, and the availability of some of the above investigation and treatment options for patients who are otherwise too ill to be moved.

Thomas Okonkwo, FRCS, FICS
Department of Orthopedic Surgery
Aderemi Aderoju, MB, FRCP
Dan Ene, MD, FRCP
Department of Medicine
Ignatius Aboh, FRCS, FICS
Department of Surgery
Samtah General Hospital
Samtah, Gizan
Saudi Arabia

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Methemoglobinemia Induced by Accidental Ingestion of Nitrite

To the Editor: Razzak[1] has described an interesting case of methemoglobinemia in a child, and discussed the pathophysiology as well as management in an instructive manner. I would like to add the following: 1) In addition to ingestion or contact, inhalation of certain oxidizing agents/chemicals or drugs may lead to life-threatening methemoglobinemia in otherwise normal individuals;[2] 2) infants under five months of age are particularly susceptible because of their physiologically low levels of NADH-dependent methemoglobin reductase;[3] 3) at the end of the case report the author mentions that methemoglobinemia should be considered in the differential diagnosis of "cyanosis not responding to oxygen therapy." In fact it should be "cyanosis not responding to 100% oxygen therapy;"[2] and 4) while dealing with a case of cyanosis or methemoglobinemia, consider the use of native medicines containing oxidizing agents, as reported by Mallouh and Sarette.[2]

P. Thirumalaikolundusubramanian
Samtah General Hospital
Samtah, Gizan
Saudi Arabia

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Reply

To the Editor: I would like to thank Dr. Thirumalaikolundusubramanian for the helpful comments on the above case report. With regards to his first point, inhalation of methemoglobinemia-producing agents is mentioned in the introduction. On the second and fourth points, I agree entirely that young infants are particularly susceptible to methemoglobinemia, and that it should certainly be considered when dealing with cyanosis after the use of native medicines. With regards to the third point, what I meant by oxygen therapy was that the patient should be given the highest concentration of oxygen possible, and for most patients this would mean an inspired oxygen approaching 100%.

Dr. Q.M. Razzaq, FRCS
32 Fuller Road, Watford
Hertfordshire WD2 5QN
U.K.

Genotyping of Hepatitis C Virus Isolates from Saudi Patients

To the Editor: We greatly appreciate Al-Ahdal et al.[1] for their genotyping work. Genotyping is primarily useful for phylogenetic and epidemiologic studies of the virus. As the genotype represents only a small portion of the viral genome, it would be unusual for the genotype to be fully informative with regards to the disease-producing potential of the viron.[2] However, the idea of the authors to associate genotyping with disease severity and management should be welcomed.

Analysis of the published studies has yielded a mixed bag of results (positive, borderline, negative and confirming), ranging from some relationship between genotype and disease, to outright rejection of any relationship between genotype and prognosis of the disease.[2] So to understand the association between genotype and disease (with reference to clinical presentation, course, response to therapy and prognosis), we have to identify a test that can define prognosis with a sensitivity and specificity of at least 95%.

A. Uma, MD
Additional Professor, Microbiology
Madurai Medical College
Madurai, India
P. Thirumalaikolundusubramanian, MD
Samtah General Hospital
Samtah, Gizan
Saudi Arabia

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Reply

To the Editor: The comments of Drs. Uma and Thirumalaikolundusubramanian related to our paper[1] are appreciated. It is generally agreed that the relationship between the clinical consequences of hepatitis C virus (HCV) infection and HCV genotypes has, thus far, eluded precise description.[2] Nevertheless, speculative conclusions have been drawn from HCV genome sequence analysis in patients with chronic HCV infection. On the other hand, some relationships between HCV genotypes and response to interferon (IFN) treatment have been demonstrated. A poor response to IFN-α was reported with HCV-1b strains identical to the prototype HCV-J and with HCV-4.[4,5] It is felt that the molecular analyses of HCV gene sequences will eventually contribute to the advancement of knowledge of viral hepatitis C, not only in the epidemiological field but in the clinical arena as well.

Mohammed N. Al-Ahdal, PhD
Department of Biological and Medical Research, MBC-03
King Faisal Specialist Hospital and Research Centre
P.O. Box 3354
Riyadh 11211, Saudi Arabia

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A Late Presentation of Postpneumonectomy Pleural Empyema and Bronchopleural Fistula

To the Editor: Bronchopleural fistula (BPF) is a rare but serious complication after pneumonectomy. The recognition and diagnosis of bronchial stump disruption can be very difficult and may lead to a delay in the management of this life-threatening condition. Modern high-technology imaging techniques, such as fiberoptic bronchoscopy, computed tomography and ventilation scintigraphy, are generally used to identify the site of persistent air leakage. Bronchography is rarely of value in detecting small leaks, but has been useful in the demonstration of large ones.[1] We would like to highlight the use of methylene blue as a safe, effective and relatively noninvasive means of confirming the diagnosis of an occult postpneumonectomy BPF with pleural empyema. Little attention has been paid to this simple bedside test since 1955, when Franz et al. reported a 33.3% yield in their 24 patients

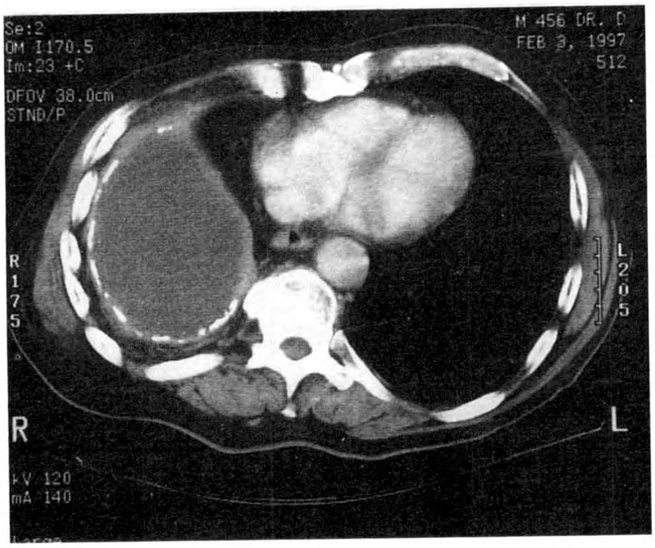

FIGURE 1. CT scan of the chest showing a right-sided pneumonectomy with mediastinal shift and a thickened pleura parietalis with calcifications.

who had pulmonary resections.[2] As most cases of postpneumonectomy BPF develop within days, weeks, or at the most, months of the operation, it should be noted that our case is an unusual late-presenting variant.[3]

In 1997, a 61-year-old man with a medical history of recurrent respiratory tract infection of the left lung was hospitalized because of malaise, weight loss and a massively productive cough. In 1990, he had undergone a right pneumonectomy because of squamous cell carcinoma of the upper lobe, with extension into the right main bronchus and postobstructive pneumonia (Stage IIIa. $T_2N_2M_0$). The postoperative recovery was uneventful. Subsequently, high-dose radiotherapy (56 Gy) was given for ipsilateral paratracheal lymph node metastases.

On admission, the patient was in poor clinical condition, although regular checkups had not demonstrated recurrence of the tumor. Physical examination revealed no abnormalities, apart from the right-sided pneumonectomy. Laboratory examination showed an ESR of 77 mm/h (n=0-15), Hb 7.6 mmol/L (n=8.7-11.2), Ht 0.40, MCV 88 fl, WBC count 12.3×10^9/L (n=4.0-10.0), with normal differentiation, total serum protein 89 g/L (n=60-80), α-1 globulin 4.5 g/L (n=1.0-4.0), α-2 globulin 11.1 g/L (n=4.0-8.0), and gamma-globulin 17.0 g/L (normal 8.0-12.0). Creatinine, urea, electrolytes, glucose and liver function tests were normal.

Chest radiography showed minor alveolar infiltration of the left lower lobe, and homogenous filling of the pneumonectomy cavity without an air-fluid pattern. Bronchoscopy did not demonstrate disruption of the bronchial stump or abnormalities in the contralateral lung. CT scan of the chest showed a pneumonectomy cavity with a thickened pleura and calcifications (Figure 1). Microscopic examination of the sputum did not reveal malignant cells or alveolar macrophages. Therefore, sinus radiography, esophagography, and CT scan of the neck were performed to exclude sinusitis, retropharyngeal abscess, Zenker-diverticula, gastroesophageal reflux, and esophagopleural fistula. Finally, transthoracic injection of 10 mL methylene blue into the pneumonectomy cavity resulted in discoloration of the sputum within a few hours, thus proving a BPF. In retrospect, the site of the BPF could not be visualized on CT scan.

The treatment consisted of surgical drainage of the cavity by a permanent open thoracostomy (Clagett procedure), parenteral broad spectrum antibiotics, and subsequent irrigation of the pneumonectomy cavity with povidone-iodine and later, sterile saline. Cultures from the pneumonectomy cavity revealed *Staphylococcus aureus* and *Streptococcus faecalis*. Eighteen months after the Clagett procedure, the patient's clinical condition remains excellent.

The incidence of postpneumonectomy BPF has decreased in recent years, but still varies around 3%.[3] It is a life-threatening condition which carries mortality rates that can reach up to 50%, depending on the onset of presentation and the presence of empyema.[4] Most deaths occur as a consequence of pneumonia, sepsis and ARDS.[4] Reported risk factors for the development of postpneumonectomy BPF are listed in Table 1.[3-5] Concomitant predisposing conditions include diabetes mellitus, hypoalbuminemia, hepatic cirrhosis, and steroid administration.[4] In our patient, four risk factors were present: right-sided pneumonectomy, lymph node dissection, radiation therapy, and preoperative pulmonary infection.

Our patient presented with the warning symptoms of fever, malaise and an increasingly productive cough, which worsened in the left lateral position. Laboratory examinations showed signs of a chronic infection. Since conventional evidence in the form of a typical air-fluid level on chest radiographs was absent, and bronchoscopy repeatedly showed no obvious defects, causes other than BPF with empyema were initially suspected. Acutely presenting postoperative BPF is commonly diagnosed by fiberoptic bronchoscopy, especially if the fistula is large and centrally located.[3] However, in patients with occult BPF it can be very difficult to localize the site of persistent air leakage.[4] In these cases, sinography (injection of radiopaque material into the pleural cavity), bronchography, ventilation scintigraphy and computed tomography are reported to be useful adjuvant techniques to support the diagnosis.[1,6,7]

In our case, the use of methylene blue proved to be a useful tool in the diagnosis of BPF after pneumonectomy. Although the instillation of methylene blue into any body cavity will result in discoloration of sputum, urine, and other secretions within 24 hours, rapid recovery of the dye from the sputum is highly suggestive of direct leakage across the bronchus stump. The question remains whether the fistula gave rise to the pleural empyema, or the pleural empyema discharged through the fistula.

Successful management of postpneumonectomy BPF

TABLE 1. *Reported risk factors for the development of postpneumonectomy BPF.*

Right-sided lung resection
Lymph node dissection
Radiation therapy
Preoperative pleuropulmonary infection
Long bronchial stump (2 cm or larger)
Stapled bronchial closure
Recurrent carcinoma
Prolonged postoperative mechanical ventilation
Pneumonectomy for chronic lung infections, e.g., tuberculosis

involves multiple steps. To limit endobronchial contamination and prevent drowning, thorough drainage of the pleural cavity, either by closed-tube or open thoracostomy, is an essential first step, followed by daily irrigations.[8,9] Excellent results can be obtained in most patients using the Clagett procedure and its modifications, in which resection of several ribs result in a permanent open thoracostomy.[8] Infection of the contralateral lung should be vigorously treated with parenteral antibiotics guided by cultures of blood, sputum and empyema fluid. Only when these conditions are achieved and the nutritional status is optimized should definitive surgical repair of the fistula be considered. This may be achieved by suture closure alone, or in combination with aggressive transposition of vascularized flaps of omentum, muscle, pericardium or pleura.[4,8,9] Patients who are poor operative candidates may be treated with endoscopically or transthoracically placed tissue glue (Histoacryl) to seal the fistula.[9,10]

Johan M. van der Klooster, MD
Albert F. Grootendorst, MD, PhD
Jan W. Brouwers, MD
Departments of Internal Medicine and
Intensive Care Medicine
St. Clara Ziekenhuis
Olympiaweg 350
3078 HT Rotterdam
The Netherlands

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Book Reviews

Campbell's Urology, 7th Edition. (3 Volume Set)

Edited by Patrick C. Walsh, Alan B. Retik and E. Darracott Vaughan. Publication: October 1997. Available from Harcourt Brace International, 24-28 Oval Road, London NW1 7DX, United Kingdom. Price: US$282.00. ISBN 0-7216-4461-9.

Since the first edition of *Campbell's Urology*, which was published and edited in 1954 by Dr. Meredith Campbell, this classic textbook has been revised many times, with marked improvements. The editors of the 7th edition are all eminent urologists who are well recognized internationally as authorities within their specialties.

The three-volume set covers all aspects of the anatomy and physiology of the urinary tract, molecular genetics and modern diagnostic and therapeutic methods and procedures as applied to the kidneys and genitourinary tract. The three volumes are comprehensive and detailed reference books with current and authoritative coverage of all areas of adult and pediatric urology. *Campbell's Urology* can be considered an "encyclopedia" of genitourinary diseases, which should be of great value to practicing urologists and to urology residents and fellows, who can refer to it for a comprehensive review of genitourinary diseases. This textbook has remained the benchmark reference book since its first edition, and should undoubtedly be available in the library of all departments of urology.

Volume 1 is divided into five sections, covering molecular genetics and anatomy, urologic examination and diagnostic techniques, renal physiology and pathophysiology, infections and inflammation of the genitourinary tract, and urine transport and voiding function and dysfunction. The chapter on principles of molecular genetics deals in depth with the historical perspective of this extremely important new subspecialty, covering the basics and the advanced strategies in molecular genetics. A comprehensive review of genes and transcription is well illustrated and easily comprehensible to the practicing urologist despite its in-depth detail, which may seem a little superfluous. However, the importance of this new field in the practice of urology, in terms of diagnosis and treatment of genitourinary cancer, should be emphasized, along with the medical value of understanding the basics of DNA-binding proteins and the tools of molecular genetics as applied clinically.

The other chapters deal with the anatomy and physiology of the genitourinary tract, as well as urological examinations and diagnostic techniques, and provide basic information, which should be of great value to residents and fellows in urology. The chapter on urinary tract imaging and intervention lacks information on some of the new radiological techniques, such as the spiral CT angiography, MRI angiography, the RAGE scan, the Prostascint and other new techniques which are becoming widely used in the diagnosis of genitourinary cancer and other renal vascular diseases. The use of MRI and color Doppler ultrasonography in the diagnosis of urethral strictures and new interventional procedures used for the relief of renal and the ureteral obstructions need to be expanded on and used to replace older methods, such as arteriography and nephrotomography. The chapter on renal physiology is a classic which should be read by all urologists, as it represents a valuable introduction to the understanding of the pathophysiology of renal diseases, namely acute and chronic renal failure and obstructive uropathy, which are explained in detail by known experts in this field. The following chapters on obstruction of the ureter and renal vascular hypertension provide new details for the diagnosis of these entities. The chapters on renal vascular surgery and renal transplantation, written by well-known authorities, comprehensively summarize the advances of modern science in those fields. The additional chapters in Volume 1 which deal with the infections and inflammation of the urinary tract, interstitial cystitis, sexually transmitted diseases, AIDS and related conditions, neurogenic vesical dysfunction, and urinary incontinence, are well written, detailed and comprehensive, and although they do not include all modern diagnostic and therapeutic procedures relating to these diseases, they nevertheless present a valuable overview of the physiology, pathophysiology, diagnosis and management of these conditions. The controversial aspects of some of these diseases preclude a full description of all the recent information which is becoming rapidly available to urologists through specialized journals and meetings.

Volume 2 of *Campbell's Urology* includes well-detailed chapters on sexual function and dysfunction, reproductive function and dysfunction, benign prostatic hyperplasia and a mini textbook on pediatric urology. The 35 chapters incorporated in this volume are written by well-known authorities and represent current information on adult and pediatric diseases, which is essential for both the trainee and practising urologist. The format of these chapters is comparable to that of Volume 1 and they expand on the anatomy and physiology of the urinary and genital tract, leading to in-depth explanations of the pathophysiology of the respective diseases and the modern methods for their diagnosis and treatment. The section on Pediatric Urology, which includes several chapters, discusses in depth the most common conditions which are of interest to the general urologist, as well as to the pediatric urologist who can benefit from the detailed information provided in these chapters. Although some advanced information which can be found in textbooks of pediatric urology may be lacking, this in no way undermines the importance of these well-written and comprehensive chapters which constitute valuable reference material on the most important aspects of pediatric urology.

Volume 3 of *Campbell's Urology* is composed of sections on oncology, urinary lithiasis, endourology and laparoscopy, and urological surgery, as applied to the whole genitourinary tract. Historical aspects, basic and clinical biology, epidemiology, etiology and risk factors, pathology, natural history, prognostic indicators, diagnosis, staging, and modern therapies, including surgery, radiotherapy and chemotherapy, are fully detailed for all neoplasms of the genitourinary tract and present the reader with an in-depth overview of different aspects of genitourinary cancers. Certain novel techniques, in terms of gene therapy and immunotherapy, are not fully covered and may be found explained in more detail in the new textbooks on genitourinary oncology. New diagnostic tests, such as the use of the PSMA and the Prostascint, are not covered in the chapter on prostate cancer, but this omission may be due to the still investigational aspect of these procedures. The chapter on urinary lithiasis presents an overview of the etiology, the epidemiologic aspects, the pathophysiology of stone formation, the clinical presentation, and the diagnosis and management of this urologic condition. Basic information and well-established methods of diagnosis and management are offered to the reader in a well-written, easy-to-read style. More detailed information on urinary lithiasis should be sought in specialized textbooks on this medical condition. The final chapters on endourology, laparoscopy and urologic surgery are well illustrated and represent state-of-the-art techniques for the surgical management of most genitourinary diseases. The illustrations, despite their good quality, do not match those found in atlases of urologic surgery, which may provide more detailed information about these techniques to residents and fellows in urology. They are, however, of great value for those urologists involved in performing these procedures, as they present, schematically and in writing, the important strategies in performing those procedures.

In summary, the 7th edition of *Campbell's Urology* represents the most comprehensive reference textbook for all genitourinary diseases. It has definitely lived up to its reputation in terms of quality and the provision of in-depth and up-to-date information on all areas of adult and pediatric urology. Its encyclopedic nature may be viewed as too detailed for the practicing urologist who is seeking more concise information regarding certain conditions encountered in his private practice. This textbook, however, is still the benchmark urology reference book, and one to which all other urology textbooks should be compared. Its availability in any medical library is essential for the optimal practice of urology. As new information becomes rapidly available in all subspecialties of urology, periodic revision of *Campbell's Urology* is of utmost importance in order to keep readers abreast of the new advances in this specialty.

Kamal A. Hanash, MD, MS, FACS
Chairman, Department of Urology, MBC-46
King Faisal Specialist Hospital and Research Centre
P.O. Box 3354
Riyadh 11211, Saudi Arabia

Brain Topography Today

Edited by Y. Koga, K. Nagata and K. Hirata. Available from Elsevier Science BV, P.O. Box 211, 1000 AE Amsterdam, The Netherlands, or from Elsevier Science Inc., P.O. Box 945, Madison Square Station, New York NY 10160-0757, USA. Price: US$293.00. ISBN 0-444-82778-2.

This book is a report on the proceedings of the third Pan Pacific Conference on Brain Topography held in Tokyo Bay, Japan, on 1-4 April 1997.

The advances in computer technology have made it possible to crunch large amounts of numeric data into visual images that are easy for the human brain to understand. The sources of data are multiple and include recorded spontaneous or evoked cerebral electrical activity (EEG and evoked potentials), recorded minute magnetic fields from the surface of the brain (MEG, or magnetoencephalogram), received signals that are emitted from protons within the brain in response to radio-frequency stimulation (MRI and fMRI), and energy generated by annihilation of positrons contained in special radiopharmaceuticals that are delivered to the entire brain or targeted to specific areas (PET), etc. Sophisticated computer algorithms have made it possible to localize such sources with precision and to display them as maps or images. The subject of the book is, therefore, a multidisciplinary look at the functions of the brain through diverse techniques unified by their ability to produce a visual end product.

The book contains over 140 articles contributed by nearly triple that number of authors. Titles range from "Event-related potentials in alternation of perceived images in binocular rivalry" to "Topographical analysis of CNV during listening to background music: rock vs. classic." Articles are grouped under 15 headings covering basic areas, such as source localization and visual information processing, or applied areas such as epilepsy, psychiatric and neurological disorders.

Proceedings are usually prepared in a hurry, with less emphasis on the quality of the print. The publisher has done an exceptional job in the quality of the print and image reproduction.

The subject is sophisticated and can be of interest to subspecialists in neurosciences, such as neurophysiologists, neuroradiologists and neuropsychologists, especially those involved in research. Considering the limited audience, the book price is not unreasonable. It should be a useful reference for researchers on the subject.

Zuheir Al-Kawi, MD, FAAN
Department of Neurosciences, MBC-76
King Faisal Specialist Hospital and Research Centre
P.O. Box 3354
Riyadh 11211, Saudi Arabia

New Trends in Cerebral Hemodynamics and Neurosonology

Edited by J. Klingelhofer, E. Bartels and E.B. Ringelstein. Available from Elsevier Science BV, P.O. Box 211, 1000 AE Amsterdam, The Netherlands, or from Elsevier Science Inc., P.O. Box 945, Madison Square Station, New York NY 10160-0757, USA. Price: US$287.50. ISBN 0-444-82361-9.

This book presents the proceedings of the 10th International Symposium on Cerebral Hemodynamics, which was held in Munich, Germany, in September 1996. The goal of the meeting was to provide an opportunity for prominent researchers in the field to define topical issues, discuss current controversies and arrive at a consensus regarding some of the more important aspects in the field of cerebral hemodynamics and sonology.

During the symposium more than 300 papers were presented by recognized leading clinicians and researchers. Roughly a hundred of these have been selected to shape the eight chapters of this book.

In almost every chapter, a review section is provided that outlines the latest information, showing that the body of knowledge is anything but static, especially when dealing with aspects and techniques, such as cerebral hemodynamics and sonology, that have advanced dramatically over the past few years.

The first chapter deals with carotid and vertebrobasilar occlusive disease and shows how in vascular work, ultrasound provides visualization of the vessel wall with a degree of detail unavailable in other modalities. In the second chapter, the authors deal with the clinical relevance of ultrasonography and other imaging techniques. They outline how ultrasonography provides an excellent temporal resolution, showing that while the spatial resolutions of these methods have limitations and are better reached with other imaging techniques, these diagnostic modalities are not alternatives to each other but may otherwise integrate. The third chapter highlights the diagnostic value of transcranial color-coded duplex imaging, the ancient dream of every neuroscientist—to explore the brain by just putting a probe on the head of the patient. Detection of the cerebral microemboli and the use of echo-contrast agents are the issues of the next two chapters, which deal with the latest application of transcranial Doppler technology. The last three chapters show how changes in the blood flow over time can best be monitored by ultrasound. In fact, evoked flow and functional testing of autoregulation that were confined to the laboratory a few years ago can now be performed at the bedside of the patient with no adjunctive risk, with the use of ultrasound technology.

The color plates are remarkable and include several examples of color-flow imaging. The text suffers only in the respect that, as is often the case in books by multiple authors, there is some redundancy and overlapping of material between chapters. It actually represents the most current knowledge in cerebral hemodynamics and sonology, considering that, as in many fields of medicine, information becomes old the moment it is written.

The book will benefit any clinical neuroscientist who cares for patients with cerebrovascular disease and any technician who performs cerebral hemodynamics studies, and most of all the veterans who may broaden their application of this technology.

Neurosonology has come of age after more than 20 years, and it seems that the field of cerebral hemodynamics is enjoying a dynamic present and can look to a bright future.

Domenico G. Iacopino, MD
Department of Neurosciences, MBC-76
King Faisal Specialist Hospital and Research Centre
P.O. Box 3354
Riyadh 11211, Saudi Arabia

The Thyroid: Fine-needle Biopsy and Cytological Diagnosis of Thyroid Lesions

Edited by S.R. Orell and J. Philips. Published by S. Kargar AG, P.O. Box CH-4009, Basel, Switzerland. For easy ordering, log on to: http://www.karger.ch. Price US$97.50. ISBN: 3-8055-6383-3

This book is the fourteenth volume in the series "Monographs in Clinical Cytology." In spite of the fact that there are only a handful of commonly encountered lesions in the thyroid, fine-needle aspiration biopsy of this organ continues to challenge the diagnostic acumen of even the best and most experienced pathologist. In this context, a monograph on the fine-needle biopsy and cytologic diagnosis of thyroid lesions written by acknowledged experts in the field is certainly welcome. The authors use the term fine-needle biopsy, as opposed to fine-needle aspiration, since they believe that biopsy without aspiration is extremely suitable for thyroid. I could not agree more.

The book consists of eight chapters. The first chapter briefly outlines the historical perspectives in the development and acceptance of the technique of fine-needle aspiration biopsy, and provides some general comments regarding the application of aspiration biopsy to the diagnosis of thyroid lesions. The next chapter deals with the histology and physiology of the thyroid. The third chapter discusses the role of fine-needle biopsy in the investigation of thyroid disease and its diagnostic accuracy. The remaining chapters discuss the fine-needle diagnosis of the various lesions, outlining the cytomorphologic features and salient diagnostic and characteristic features of the various lesions. These features are nicely summarized in the last chapter for quick reference.

I found the book to be easily readable, since cytologic descriptions are always correlated with histologic parameters. This helps to translate the cytologic findings into more familiar histologic patterns of the thyroid lesions. The discussion of various entities is detailed but proportional to their frequency and clinical significance. The chapters are profusely illustrated, and the overall quality of the photomicrographs is good. I was, however, a bit disappointed to see that color pictures were only limited to three pages, while the rest were black and white. I believe the usefulness of this book would have been markedly enhanced if all or most of the photomicrographs were in color. There are 231 references, which were well chosen and up to date. The printing and binding are of excellent quality and the price appears reasonable.

The book will be extremely useful for all pathologists who practice aspiration biopsy and also for fellows and residents who are in the process of learning to perform and interpret fine-needle biopsy of the thyroid.

Mohammed Akhtar, MD, FCAP
Head, Division of Anatomic Pathology
Department of Pathology and Laboratory Medicine, MBC-10
King Faisal Specialist Hospital and Research Centre
P.O. Box 3354
Riyadh 11211, Saudi Arabia

Rypin's Intensive Reviews: Pathology (1998)

Edited by I. Damjanov, P.B. Conran and P.J. Goldblatt.
Published by Lippincott-Raven Publishers, 227 East Washington Square, Philadelphia, PA 19106, USA.
Price US$23.00. ISBN: 0-397-51555-3.

This book, which is part of the Rypin's basic sciences intensive review series, is intended primarily for medical students and new graduates of medicine who are preparing for the United States Medical Licensing Examination (USMLE), Step 1. It is a concise but well-written book which covers only the most important aspects of pathology, and concentrates on key concepts and cardinal diseases. It is, therefore, not a substitute for major pathology textbooks.

The book also includes 220 questions, which are similar to the USMLE format. These questions are followed by short discussions and explanations that provide the students with a rapid assessment of their knowledge of pathology. The following minor points of criticism should, in my opinion, be mentioned: 1) A short chapter of introduction to the science of pathology is lacking from this review book. This chapter should contain essential information on the scope and techniques of pathology, clinicopathological integration and the "art" of making diagnoses. An account of the role of autopsies in the study of diseases, auditing of clinical diagnosis, education and research, should also be included (albeit briefly) in this introduction. 2) The chapters on inflammation, neoplasia, lymphomas, diseases of the thymus and cardiovascular system are too brief for comfort, and a slight expansion would have been advantageous. 3) I would have preferred to see several multiple-choice questions at the end of each chapter, in addition to a collection of questions forming one or more comprehensive mock examinations at the end of the book.

Despite the above, I have no hesitation in recommending this book, which is reasonably priced and clearly written, to all medical students and graduates of medicine who are preparing for the USMLE or Canadian examination.

A.C. Al-Rikabi, MD, FRCPath, FIAC
Department of Pathology (32)
King Saud University
P.O. Box 2925
Riyadh 11461, Saudi Arabia

ANNOUNCEMENTS

FELLOWSHIPS AND TRAINING PROGRAMS

King Faisal University, College of Medicine and Medical Education, Short Courses 1998-1999

The Directorate of Medical Education at King Faisal University would like to announce the dates of their short courses for 1998-1999. Basic Surgical Skills: 18 November 1998; Basic Course in Healthcare Quality Management: 21 November-16 December; Quality and Standards in Assessing Student Learning: 24-26 November; Percutaneous Dilatation Tracheostomy: 26 November; Preparatory Course for the National Center Agency for Medical Laboratory Personnel: 3 and 6 December; Research Methodology: 5-9 December; International Health: 12-16 December; Neurological Development Training: 12-23 December; Mobilization of Peripheral Joints: 14-15 December; Advanced Trauma Life Support: 17-19 December; Environmental Health: 19-23 December; Basic Course in Healthcare Quality Management: 23 January-17 February 1999; Symposium & Workshop on Stereotactic and Endoscopic Methods in Neurosurgery: 26-27 January; Advanced Biochemical Genetics: 6 February; Course in Applied Basic Science for Surgical Resident (10 weeks): 6 February; Advanced Trauma Life Support: 16-18 February; Update in Internal Medicine: 17-18 February; Basic Ultrasound in Obstetrics and Gynecology: 20-22 February; Teaching Skills for Physician Educator: 23-25 February.

First Year Fellowship in Pediatric Surgery at KFSH&RC

King Faisal Specialist Hospital and Research Centre has an opening for a first year fellow in their Pediatric Surgery Training Program. The program is intended for surgeons who have completed their surgical training and wish to subspecialize in Pediatric Surgery. The applicant must have successfully completed training in an accredited general surgical residency training program, with progressive responsibility. Board certification by the Saudi Board or an equivalent certification is mandatory. The Surgical Fellowship program will provide the successful fellow with three years of training. The fellow will rotate through General Surgery and Urology, and may spend some time in other sections in the hospital. For further information, please contact Academic Affairs and Postgraduate Education, King Faisal Specialist Hospital and Research Centre, MBC 36, PO Box 3354, Riyadh 11211, Saudi Arabia. Tel: 966-1-464-7272, ext. 31834; fax: 966-1-442-7237.

Postgraduate Training Program in Palliative Care

The Oncology Department of King Faisal Specialist Hospital and Research Centre invites applications for a full-time Postgraduate Training Program in Palliative Care Medicine. Palliative Care is a new specialty in medicine, dealing with patients who are no longer responsive to curative therapies. The majority have cancer. The program provides specialty experience for one year at KFSH&RC, followed by advanced specialty training overseas, in Europe, North America, or Australasia. The training program will be for a minimum of three years, but may be extended by agreement.

Applicants must be Saudi Nationals, and have completed training in an appropriate specialty, e.g., internal medicine, family medicine, anesthetics, oncology, or surgery, and have passed the Arab Board certifying examination or its equivalent. The position is suitable for both male and female doctors.

For further information, please contact: Director, Academic Affairs and Postgraduate Education, MBC 36, King Faisal Specialist Hospital and Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia. Tel: 966-01-442-7214; fax: 966-01-442-7237.

Saudi Board of Neurology

King Faisal Specialist Hospital and Research Centre is pleased to announce the launch of the Saudi Board of Neurology. This is a nationwide program under the guidance and supervision of the Saudi Council for Health Specialties. It is a four-year training program, comprising one year of internal medicine, followed by three years of neurology in an accredited center.

Candidates are now being recruited. For further information, please contact the office of Academic Affairs and Postgraduate Education, King Faisal Specialist Hospital and Research Centre, P.O. Box 3354, Riyadh 11211, Saudi Arabia. Tel: 966-01-464-7272, ext. 31834; fax: 966-1-442-7237.

Pediatric Neurology Fellowship Program

King Faisal Specialist Hospital and Research Centre invites applicants for its Pediatric Neurology Fellowship Program. This is a 3-year fellowship training program, with two years spent in Riyadh and one year abroad. Applicants must have successfully completed training in an accredited residency training program, and successfully passed the Pediatric Arab Board certifying exam or its equivalent. For further information, please contact Academic Affairs and Postgraduate Education, King Faisal Specialist Hospital and Research Centre, MBC 36, PO Box

3354, Riyadh 11211, Saudi Arabia. Tel: 966-1-464-7272, ext. 31834; fax: 966-1-442-7237.

Postgraduate Training Program in Anesthesiology

The Anesthesiology Department of King Faisal Specialist Hospital and Research Centre is pleased to invite applications for its postgraduate training program in Anesthesiology. The course will involve one year of training at KFSH&RC, and a four-year residency training period in North America. For further information, please contact Academic Affairs and Postgraduate Education, King Faisal Specialist Hospital and Research Centre, MBC 36, PO Box 3354, Riyadh 11211, Saudi Arabia. Tel.: 966-1-464-7272, ext. 31834; fax: 966-1-442-7237.

SYMPOSIA, MEETINGS AND CONFERENCES

Fine Needle Aspiration and Cervical Cytology Workshop

A Fine Needle Aspiration and Cervical Cytology Workshop will be held from 10-12 November 1998 (21-23 Rajab 1419) in the Research Center at King Fahad Hospital in Jeddah. The workshop will concentrate on the common diagnostic cytology problems encountered by the pathologist in everyday practice. This workshop is suitable for pathologists, trainees in pathology, cytotechnology, as well as obstetrics and gynecology. Fees will be SR300 for pathologists and SR100 for residents, trainees and cytotechnologists. Mail registration and payment by bank draft to: Medical Outreach Program, MBC 80, King Faisal Specialist Hospital and Research Centre, PO Box 3354, Riyadh 11211, Saudi Arabia. Tel: 966-01-442-4251; fax: 966-01-443-4280.

Sixth International Congress of the Middle East Society for Organ Transplantation (MESOT)

The Sindh Institute of Urology and Transplantation (SIUT) will host the Sixth International Congress of the Middle East Society for Organ Transplantation in Karachi, Pakistan, from 13-16 November 1998 (24-27 Rajab 1419). For further information, contact: Secretariat, Sindh Institute of Urology and Transplantation, Dow Medical College and Civil Hospital, Karachi 74200, Pakistan. Tel: 92-21-773-0351, 773-0387, and 772-4922; fax: 92-21-773-7436, 776-6212. E-mail: info@siut.org or Symp@-siut.khi.sdnpk.undp.org. Website: http://www.siut.org.

Third International Symposium on Urology, Nephrology and Transplantation of SIUT

The third International Symposium on Urology, Nephrology and Transplantation of the Sindh Institute of Urology and Transplantation (SIUT) will be held in Karachi, Pakistan, from 16-18 November 1998 (27-29 Rajab 1419). For further information, contact: Secretariat, Sindh Institute of Urology and Transplantation, Dow Medical College, Karachi 74200, Pakistan. Tel: 92-21-773-0351, 773-0387, and 772-4922; fax: 92-21-773-7436, 776-6212. E-mail: info@siut.org or Symp@siut.khi.sdnpk.undp.org. Website: http://www. siut.org.

The First Arab International Congress/Exhibition on Cancer

The First Arab International Congress/Exhibition on Cancer is to be held in Dubai (United Arab Emirates) at the Le Meridien Beach Hotel from 16-20 November 1998 (27 Rajab-1 Shaban 1419). The aim of the Congress is to bring a maximum number of scientists and clinicians from the Arab world into contact with their colleagues from other parts of the world. The theme of the Congress will be the Molecular and Clinical Advances in Cancer, and will feature topics such as the Molecular Biology of Cancer, Molecular Genetics of Cancer, Molecular Diagnostics and Clinical Trials and Cancer Therapy. About 500 scientists and clinicians, in addition to health care professionals and decision-makers from the Arab region, are expected to attend the meeting. For further information on registration, contact: The Organizer, P.O. Box 54123, Dubai, UAE. Fax: 971-4-499-482. E-mail: merzak@gulfnetce.com.

Fourth Saudi School on Human Molecular Genetics

The Fourth Saudi School on Human Molecular Genetics will be held at the Department of Medical Biochemistry and the WHO Collaborating Center, King Saud University, Riyadh, Saudi Arabia, from 28 November-3 December 1998 (9-14 Shaban 1419). The course will include lectures, demonstrations, hand-outs and a round table discussion. For further information, please contact the Organizer, Department of Medical Biochemistry and the WHO Collaborating Center, or the Postgraduate Center, College of Medicine, King Saud University, P.O. Box 2925, Riyadh 11461, Saudi Arabia. Tel: 966-1-467-0831/467-1551; fax: 966-1-467-2575/481-1853.

The Society of Obstetricians and Gynecologists of Canada

The Society of Obstetricians and Gynecologists of Canada wishes to publish the following list of its upcoming 1998-1999 Continuing Medical Education conferences (CMEs): 1) The Ontario CME will be held from 3-5 December 1998 (14-16 Shaban 1419) at the Toronto Marriott, Toronto, Ontario; 2) The International CME will be held from 7-11 March 1999 (19-23 Dhu Al-Qada 1419) at the Rex Grenadian, Grenada; 3) The West/Central CME will be held from 25-29 March 1999 (8-12 Dhu Al-Hijja 1419) at the Rimrock Resort Hotel at Banff, Alberta; 4) The 55th Annual Clinical Meeting (ACM) will be held from 25-29 June 1999 (12-16 Rabi Al-Awal 1420) at the Ottawa Congress Center, Ottawa, Ontario; and 5) the FMC Québec will be held from 30 September to 2 October 1999 (21-23 Jumada Al-Thani 1420) at the Hotel Mont Gabriel, Québec. For more information, contact Jennifer Brown, Administrative Assistant, Education Division, The Society of Obstetricians and Gynecologists of Canada, 774 Promenade, Echo Drive, Ottawa, Ontario K1S 5N8, Canada. Tel: 613-730-4192, or 1-800-561-2416; fax: 613-730-4314. E-mail: jbrown@sogc.com.

Fundamental Critical Care Support (FCCS) Course

King Khalid University Hospital and King Saud University, in collaboration with the Society of Critical Care Medicine (SCCM) of the USA, will hold a two-day comprehensive course on 8-9 December 1998 (19-20 Shaban 1419) at the King Khalid University Hospital. The FCCS program will be beneficial to health care providers without formal critical care training, including physicians and nurses who care for the critically ill, primary care physicians and emergency physicians. The course will address fundamental management principles for the first 24 hours of critical care. A certificate of successful completion will be issued by SCCM (USA). For more information, please contact Lita Plazuela, KKUH, College of Medicine, Postgraduate Center, P.O. Box 2925, Riyadh 11461, Saudi Arabia. Tel: 966-01-467-1554, 467-1556; fax: 966-01-481-1853.

Arab Health IT '98

IIR Exhibitions is organizing the Arab Health IT '98 along with the Arab Health show at the Dubai World Trade Center, from 8-11 December 1998 (19-22 Shaban 1419). This is a new professional exhibition dedicated to international telemedicine and healthcare IT systems and solutions management. The show is aimed at attracting specialists interested in applying the latest IT systems applications and telemedicine tools to their particular medical disciplines. At the show, providers of medical information will demonstrate their expertise, discuss opportunities and evaluate new concepts. For further information, please contact: Barbara Saunders, MCS-Marketing Communications Services, P.O. Box 20970, Dubai, United Arab Emirates. Tel: 0097-1-445-2126; fax: 0097-1-446-0926. E-mail: mcsdubai@emirates.net.ae.

Iraq Medihealth '98

The Iraq Doctors' Syndicate is organizing Iraq Medihealth '98, the Iraq International Medical, Healthcare and Pharmaceutical Exhibition, from 12-15 December 1998 (23-26 Shaban 1419), at the Baghdad International Exhibition Center. For more information on this event, please contact the International Sales Office: Ramzi Aydi, Jordan Trade and Graphics Center, P.O. Box 950708, Amman 11195, Jordan. Fax: 962-6-568-8108, or e-mail: jtgc@cns.go.com.jo.

10th Scientific Session of the Saudi Heart Association

The Saudi Heart Association will hold its 10th Scientific Session on 23-25 Shawwal 1419 (9-11 February 1999) at the King Saud University, Riyadh, Saudi Arabia. This scientific conference, organized annually by the Association, will bring cardiovascular experts and specialists from around the world to discuss recent developments in cardiovascular medicine. Interested overseas participants must obtain visa information from the Saudi Embassy or Consulate office in their country.

Additional information regarding submission of abstracts may be obtained from the Saudi Heart Association, College of Medicine, King Saud University, P.O. Box 2925, Riyadh 11461, Saudi Arabia. Tel: 966-1-467-1556/1554; fax: 966-1-467-2553/1853.

First Annual Hematology and Blood Transfusion Meeting

The Postgraduate Centre and the Division of Hematology, College of Medicine, King Saud University, Riyadh, wishes to announce the "First Annual Hematology and Blood Transfusion Meeting" to be held in Riyadh, on 7-9 February 1999 (21-23 Shawwal 1419). The topics at the meeting will include: leukemias, acquired anemias, bone marrow transplantation, blood transfusion, thrombophilia, hemophilia, hemoglobinopathies, hematological malignancies, and hemostasis. Distinguished hematologists have been invited to give lectures. Abstracts or papers for presentation (either oral or poster) are being accepted, and must be received by the Organizing Committee no later than 30 November 1998 (11 Shaban 1419). For further information, please contact Postgraduate Centre, College of Medicine, King Saud University, P.O. Box 2925, Riyadh 11461, Saudi Arabia. Tel: 966-1-467-1551, 467-1556, 467-1564; fax: 966-1-481-1853.

The Fourth Scientific Conference

The Saudi Society of Family and Community Medicine, with the cooperation of the Directorate of Health Affairs in

Makkah, announces the Fourth Scientific Conference, to be held in Makkah from 1-3 March 1999 (13-15 Dhu Al-Qa'da 1419). The focus of the conference will be Early Detection and Periodic Health Assessment. The topics for selection include: 1) The concept of early detection and periodic health assessment; 2) Regional and global experiences; 3) Saudi experience; 4) Targeted groups and services; 5) Social and ethical domains; 6) Economic issues in early detection and periodic health assessment; and 7) Role of the private sector in early detection and periodic health assessment. For further information, contact: Scientific Committee, Makkah Office - Saudi Society of Family and Community Medicine, P.O. Box 9195, Makkah, Saudi Arabia. Tel: 966-2-548-0853/542-1564; fax: 966-2-542-0542.

International Symposium on Recent Advances in Pediatrics and Neonatology

The Medical Services Division of the Ministry of Defence and Aviation is organizing an International Symposium on Recent Advances in Pediatrics and Neonatology, at the King Fahad Military Medical Complex, in Dhahran, Saudi Arabia on 2-4 March 1999 (14-16 Dhu Al-Qa'dah 1419). Topics to be discussed include child abuse, infectious diseases, vaccinations, genetics, sickle cell anemia, perinatology and neonatology. In addition, there will be workshops on sickle cell disease, diabetes, cardiology, nephrology, asthma, and neonatology. International speakers at the Symposium will include Prof. Robert Leshnar (USA), Prof. Victor Yu (Australia), Dr. Anne Nesbitt (UK), and Dr. Mariam Rajab, in addition to other national speakers. All pediatricians and neonatologists are invited to submit papers for presentation, posters, or video sessions. The time allowed for oral presentation will be 15-20 minutes. The abstracts should be typewritten, single-spaced on an A4 sheet of plain paper, and should contain no more than 250 words. The deadline for receiving the abstracts is 2 December 1998 (13 Shaban 1419). For a pre-registration form or to send an abstract, contact: Dr. Khalid Danish, King Fahad Military Medical Complex, P.O. Box 1300, Dhahran 31392, Saudi Arabia. Fax: 966-3-844-1247, or 966-3-840-5021.

First Arab Regional Conference of Rehabilitation & 2nd Gulf Conference in Medical Rehabilitation

The First Arab Regional Conference of Rehabilitation & the 2nd Gulf Conference in Medical Rehabilitation will be held in Safat, Kuwait, on 22-25 March 1999 (5 to 8 Dhu Al-Hijja 1419). Deadline for abstracts is 6 January 1999.

For more details, please contact: The Conference Secretariat, P.O. Box 4070, 13041 Safat, Kuwait. Tel: 965-487-0406; fax: 965-487-4190.

Practical Pulmonary Pathology, Imperial College School of Medicine, London

The Imperial College School of Medicine will hold a "hands-on" course on Pulmonary Pathology in London, on 14 and 15 April 1999 (28 and 29 Dhu Al-Hijjah 1419). This course is separate from, but complements, an IAP course that will be held in Swansea on the following two days. Lectures will be limited to three each day, and guest lecturers include T. Colby (Mayo Clinic), J.M. Kay, (McMaster University), and W. Travis (Armed Forces Institute of Pathology). Application forms may be obtained from Professor B. Corrin, Brompton Hospital, London SW3 6NP. Fax: 44-171-351-8293; e-mail: b.corrin@-ic.ac.uk (with copy to: l.oscar@ic.ac.uk).

The European Association for Cardio-Thoracic Surgery

The European Association for Cardio-Thoracic Surgery (EACTS) is to hold its 1999 meeting in Edinburgh, Scotland, from 19-22 September 1999 (10-13 Jumada Al-Thani 1420).

For further information contact: Torkel Aberg, Secretary-General, EACTS. Fax: 46-90-785-36-01, or e-mail: eacts.secretary@mailbox.calypso.net.

First Regional Symposium and Workshop on Ethical and Genetic Counselling Issues

The Department of Medical Biochemistry and the WHO Collaborating Center of the King Saud University are organizing the First Regional Symposium and Workshop on Ethical and Genetic Counselling Issues. The Symposium will be held from 27 to 28 November 1999 (19-20 Shaban 1420), and the Workshop from 29 November to 3 December 1999 (21-25 Shaban 1420), at the Main Auditorium, College of Medicine, King Saud University, Riyadh, Saudi Arabia. The main topics to be discussed at the symposium/workshop will include: principles of genetic counselling; genetic counselling in clinical practice; genotype-phenotype correlation and variations in health and disease; strategies of control and prevention of genetic diseases; and views towards reproductive issues. For further information and abstract/visa application forms, please contact the Organizer, Department of Medical Biochemistry and the WHO Collaborating Center, or the Postgraduate Center, College of Medicine, King Saud University, P.O. Box 2925, Riyadh 11461, Saudi Arabia. Tel: 966-1-467-0831/467-1551; fax: 966-1-467-2575/481-1853.

المرضى والطرق: تمت دراسة ٢٢٠ حالة سبق تشخيص حالتهم بإجراء خزعة للعقد اللمفية. كان ١٦٤ من هؤلاء مصابين بأمراض حميدة في العقد اللمفية، بينما كان ٥٦ منهم مصابين بأمراض خبيثة. تمت مراجعة ملفات المرضى واستخدام نموذج تحوّف لوجستي لمعرفة العلامات الجسدية والفحوصات البسيطة التي سوف تتنبأ بالخباثة العقدية.

النتائج: اتضح أن هناك علاقة متبادلة بين قوام العقد اللمفية الصلب، اختبار مانتو السلبي والنتائج الإيجابية لتصوير البطن بالصدى (ظهور تضخم في الطحال والكبد مع وجود اعتلال عقدي لمفاوي أو بدونه) وزيادة احتمال وجود خباثة عقدية.

الخاتمة: اقترحنا نموذج تحوّف لوجستي لحساب احتمال وجود خباثة عقدية لمفية على اختلاف الأعمار والأجناس، وعلاقة ذلك مع قوام العقد اللمفية، اختبار مانتو ونتائج تصوير البطن بالصدى.

الكلمات المفتاحية: عقد لمفية، اختبار مانتو، تصوير البطن بالصدى: العقد الصلبة.
المدونات الطبية السعودية ١٩٩٨،١٨ (٦): ٥١٨-٥٢١.

دراسة عن مدى انتشار الصداع والشقيقة بين الأطفال في سن المدارس بالإمارات العربية المتحدة

مقدمة: يهدف هذا التقرير إلى دراسة مدى انتشار الصداع والشقيقة بين الأطفال في سن المدرسة بالإمارات العربية المتحدة، وتحديد العلاقة بين الصداع والعوامل المختلفة، مع التركيز على الشقيقة بشكل خاص، وكذلك مدى تأثير الصداع على حضور الأطفال للمدرسة.

المواد والطرق: أجريت دراسة سكانية عرضية المقطع في الفترة ما بين أكتوبر ١٩٩٥م ويونيو ١٩٩٦م. تم اختيار المشاركين في الدراسة بعد تقسيم الأطفال إلى عدة فئات مختلفة المراحل. وجمعت المعلومات عن طريق توزيع استفتاءات تبعها لقاءات سريرية. كان الأطفال من ١٢ مدرسة ابتدائية في كل من مدينة العين ودبي والشارقة بالإمارات، فكان مجموع هؤلاء الأطفال ١١٥٩.

النتائج: تقدر نسبة انتشار الصداع بـ ٣٦,٩٪، والشقيقة بـ ٣,٨٪. أظهرت الدراسة أن نسبة الصداع تزداد بازدياد العمر حيث كانت أعلى نسبة بين الأطفال ذوي ١٣ سنة (١٧,٥٪).

الخاتمة: كانت نسبة انتشار الصداع والشقيقة في دراستنا مشابهة للنسبة في أماكن أخرى من العالم. ربما تؤثر العوامل الثقافية والاجتماعية في مدى الانتشار في هذه المنطقة.

المدونات الطبية السعودية ١٩٩٨،١٨ (٦): ٥٢٢-٥٢٤.

تضيّق الأبهر:

دعوة للاكتشاف المبكر

مقدمة: يمتاز الإصلاح المبكر لتضيق الأبهر (ت أ) بقلة المضاعفات قبل العملية الجراحية وتحقيق نتائج أفضل على المدى الطويل. ولذا، فإن اكتشاف وعلاج مرضى ت أ في وقت مبكر أمر مرغوب فيه للغاية. كان الهدف من الدراسة هو مراجعة نظام الإحالة لدينا، ومعرفة مدى فعالية الفحص الاستقصائي للمواليد، وتوعية الأطباء حول هذا الشذوذ، ونمط الأعراض وسن ظهورها، والفروق في الأعراض بين ت أ المنفرد والمصحوب بآفات قلبية أخرى.

المرضى والطريقة: أجريت هذه الدراسة على ملفات ٦١ مريضا أدخلوا مستشفانا خلال الفترة بين يناير ١٩٨٩ وديسمبر ١٩٩٦م، وتبين أنهم يُعانون من ت أ. أجري تحليل لبيانات الإحالة وقورنت بنتائج التقييم القلبي في المستشفى.

النتائج: أحيل المرضى كلهم بعد ظهور الأعراض دون أن يكون هناك اشتباه بتضيق الأبهر لدى أي منهم. أحيل مريض واحد من قبل أخصائي أطفال في عيادة خاصة، والمرضى الآخرون من قبل أخصائيي الأطفال في المستشفى. ورد تعليق على النبض الفخذي والنفخة القلبية في ثلاثة خطابات إحالة فقط، في حين لم يرد أي تعليق على فارق الضغط الانقباضي (ف ض إ) بين الطرفين العلويين والطرفين السفليين وارتفاع الضغط الانقباضي في أي من خطابات الإحالة. كان ف ض إ يزيد على ١٠ ملم زئبق وكان هناك ارتفاع في الضغط الانقباضي لدى ما نسبته ١٠٠٪ و٥٨٪ من المرضى على التوالي لدى التقييم في مركزنا. كان ف ض إ لدى مرضى ت أ المصحوب بآفات قلبية أخرى أقل بدرجة مهمة مما هو لدى مرضى ت أ المنفرد.

الخلاصة: توجد حاجة ماسة لزيادة توعية أطباء الصحة الأولية بأهمية الفحص الاستقصائي للمواليد بشكل عام وقياس ضغط الدم في الأطراف بشكل خاص من أجل اكتشاف ت أ باكرا. يوصى بتوقيت الفحص الاستقصائي للمواليد بين اليوم الثالث والأسبوع الثالث. إن ف ض إ هو طريقة موثوقة للكشف عن ت أ، وهو في المدى الهام الأدنى (≤ ١٠ملم زئبق) يكون مصحوبا بآفة قلبية معقدة وليس منفرداً.

المدونات الطبية السعودية ١٩٩٨؛١٨ (٦): ٥١٤-٥١٧.

نموذج تحوّف للتنبؤ بالخباثة العقدية عند مرضى الاعتلال العقدي اللمفاوي

مقدمة: تتسبب الأمراض الحميدة والخبيثة في حدوث الاعتلال العقدي اللمفاوي. نحاول في هذا النموذج تعيين الاستقصاءات التي تتنبأ بزيادة احتمال وجود خباثة عقدية.

٢٪ من الحالات الـ ٢٦٢ الأولى، بينما كانت النسبة الإجمالية الملاحظة في ١٠٠٠ عينة هي ٠,٥٪. تمت ملاحظة الفسيفسائية المستوى الثاني في نسبة ٠,٨٪ والفسيفسائية المستوى الثالث في نسبة ٠,٩٪ من الحالات على التوالي. بلغت النسبة الإجمالية للفقدان الحملي للأحمال ذات الصبغية الطبيعية في الأسبوع الثامن والعشرين من الحمل نسبة ٢,٨٪. لم نلحظ عيوب أطراف قصيرة في أي من الأجنة بعد أخذ عينة الزغابة المشيمائية.

الخلاصة: تشير سجلاتنا إلى أن الفنيين من ذوي الخبرات الواسعة يمكن أن يجروا عينات زغابة مشيمائية بصورة آمنة وموثوقة.

المدونات الطبية السعودية ١٩٩٨،١٨ (٦): ٥٠٦-٥١٠.

تقييم مؤشرات التكهن بتحصي المرارة قبيل استئصال المرارة عبر منظار جوف البطن

الخلفية: يهدف هذا التقرير إلى دراسة مدى حساسية مؤشرات التكهن بحصى القناة الصفراء، وإزالتها عبر التنظير الداخلي قبل استئصال المرارة عبر تنظير جوف البطن.

المرضى والطرق: أجريت دراسة مراجعة على ١٤ مريضاً ممن أجري لهم بنجاح تخطيط معثكلي وعائي صفراوي راجع بالمنظار قبل استئصال المرارة عبر تنظير جوف البطن بمركز الرياض الطبي في الفترة ما بين ١٩٩٢م و ١٩٩٤م (١٤١٢هـ - ١٤١٤هـ). وتم استخدام ست مؤشرات - اليرقان، التهاب المعثكلة المراري، حصى في القناة الصفراء بتخطيط الصدى، توسع القناة الصفراء (يتجاوز ٧ ملم) بتخطيط الصدى، توسع القناة الصفراء واختلال في وظائف الكبد، واختلال نتائج اختبار وظائف الكبد دونما يرقان - لاشتباه تحصي المرارة وإزالتها عبر التنظير الداخلي قبل استئصال المرارة عبر منظار جوف البطن.

النتائج: كانت تكهنات الإصابة بحصى في القناة الصفراء بتخطيط الصدى لدى ٧٥٪ سليمة، تلاها توسع القناة الصفراء مع اختلال نتائج اختبار وظائف الكبد (٤٠٪). كما كانت مؤشرات اليرقان السريري والتهاب المعثكلة المراري متعادلة الحساسية (٤٢٪ لكل على حدة). وبلغت حساسية توسع القناة الصفراء فقط بتخطيط الصدى للتكهن بوجود حصى في القناة ٣٦٪ في حين أن اختلال وظائف الكبد دونما يرقان كان أقل المؤشرات حساسية حيث بلغ (٢٢٪). وبوجه عام، فقد أسهمت هذه المؤشرات بتشخيص حالات حصى القناة الصفراء بصورة سليمة لِـ ٣٤٪ من المرضى.

الخاتمة: ستساعد هذه المؤشرات في انتقاء المرضى المصابين بحصى في القناة الصفراء لإزالتها قبل القيام بتدخل جراحي وذلك لحين انتشار استقصاء القناة الصفراء عبر تنظير جوف البطن أو التشخيص بالطرق غير الباضعة كالتخطيط المعثكلي الوعائي الصفراوي بالرنين المغناطيسي على نطاق واسع. كما اقترح آخرون دمج هذه المؤشرات لتحسين قيمة التكهن.

المدونات الطبية السعودية ١٩٩٨،١٨ (٦): ٥١١-٥١٣.

الهدف: كان الهدف من هذه الدراسة تحديد معدل انتشار اللولبية البوابية لدى مرضى عسر الهضم الكويتيين الذين يحالون للتنظير الداخلي لمعرفة ما إذا التقصي السكاني والسريري، ووجود العصيات اللولبية، يساعد في التمييز بين المرضى الذين يعانون من مرض هام في المعدة والعفج، ومرضى عسر الهضم غير القرحي.

المرضى والوسائل: أجري اختيار عشوائي لمئتي مريض كويتي أحيلوا للتنظير الداخلي بغية تقييم حالاتهم. كما أجريت لكل مريض مقابلة شخصية مُفصلة للتعرف على السمات السكانية والسريرية، تلاها تنظير العفج والمعدة والمريء. أخيراً أخذت خزعات من مخاطية غار المعدة لتحديد وجود اللولبية البوابية. ثم قمنا بعد ذلك بدراسة البيانات التي حصلنا عليها.

النتائج: كانت نتائج التنظير الداخلي الطبيعية (٣٢٪)، التهاب غار المعدة غير المؤتكل (٢٦٪)، التهاب العفج (١٧,٥٪)، القرحة العفجية (١١,٥٪)، البصلة المشوهة (٤٪)، التهاب المريء (٧٪)، والتهاب المعدة المؤتكل (٢٪). لم يكن هناك ارتباط بين السمات السكانية والسريرية للمرضى وبين نتائج التنظير الداخلي. بلغ معدل انتشار اللولبية البوابية (٨٨,٥٪). لم تكن هناك فروقات إحصائية هامة في معدل انتشار اللولبية بين المرضى اللذين تفاوتت نتائج التنظير الداخلي لديهم.

الاستنتاج: يعتبر الخمج باللولبية البوابية منتشراً بين مرضى عسر الهضم الكويتيين الذين أحيلوا للتنظير الداخلي، بغض النظر عن سماتهم السكانية والسريرية أو السبب المستبطن لعسر الهضم لديهم. لا تشكل الوسائل غير الباضعة بديلاً عن التنظير الداخلي للكشف عن العصيات اللولبية لدى استقصاء حالات عسر الهضم.

المدونات الطبية السعودية ١٩٩٨،١٨ (٦): ٥٠٢-٥٠٥.

تقييم وراثي خلوي لألف عينة من الزغابات المشيمائية

الخلفية: يتم أخذ عينة من الزغابة المشيمائية روتينياً لتشخيص النمط النووي الجنيني في الثلث الأول من الأحمال المحفوفة بالمخاطر. يعتمد نجاح الإجراء على خبرة الفني الذي يقوم بالإجراء. إن الغرض من هذه الدراسة هو تحديد العلاقة بين مختبر يتم ضبطه سريريا بواسطة فني وسلامة وموثوقية إجراء عينة الزغابة المشيمائية.

المرضى والطرق: أخذت عينة زغابة مشيمائية من ألف مريضة يعانين من أعراض متنوعة مثل حامل مسنة أو طفل سابق يعاني من عيوب صبغية، .. الخ. أجرينا عمليات عبر عنق الرحم وعبر البطن، حسب موقع المشيمة ومحيط الرحم. بالنسبة للتشخيص الوراثي الخلوي أجرينا مستنبتات مباشرة وقصيرة المدى حسب البروتوكول القياسي للمختبر.

النتائج: تم التوصل لنتائج وراثية خلوية في نسبة ٩٩,٦٪ من الدراسات بنتائج إيجابية بلغت نسبتها ٩٤,٥٪ (٤٦,XX أو ٤٦,XY) أما النسبة المتبقية فكانت فيها عيوب صبغية بنيوية وعددية متنوعة. تم تحديد التلوث بخلايا الأم في نسبة

الأبواغ الفطرية "الترناريا" المحمولة بالهواء: محسسات أرجية محتملة في المملكة العربية السعودية

الخلفية: من أجل استقصاء دور أنواع الفطريات "ألترناريا" المحمولة بالهواء في تحسيس الأشخاص الذين يعانون من أعراض أرجية تنفسية، خصوصاً الربو القصبي، أجريت دراسة حيهوائية وسريرية (تشخيصية) في عدة مراكز في المملكة العربية السعودية.

المواد والطرق: تمت دراسة أبواغ "ألترناريا" المنقولة بالهواء في أربعة مراكز مختلفة في الرياض وجدة والخبر، وتضمنت ثلاث سنوات في موضع واحد. أجريت اختبارات الوخز الجلدي على ما مجموعه ٦١٦ شخصاً أرجياً يراجعون عيادات الحساسية في ستة مستشفيات مختلفة في مناطق أبها والقصيم وجيزان وجدة والهفوف ومكة المكرمة.

النتائج: شكلت أبواغ "ألترناريا" نسبة تتراوح بين ١,٩٪ و ٩,٦٪ من إجمالي الأبواغ الموجودة في الهواء، وتجاوز التركيز الأقصى ١٠×٥،١ ^{٢} بوغاً لكل متر مكعب من الهواء في جدة، تبعه على الترتيب ١٠×٤,٩ ^{٢} بوغاً لكل متر مكعب في الخبر. تقلب متوسط التركيز الأسبوعي والشهري لأبواغ "ألترناريا"، حيث وصل إلى ١٥٠ بوغاً/متر مكعب و ٦٠ بوغاً/متر مكعب على التتالي. تم أيضاً تسجيل اختلافات إقليمية كمية. نتج عن التفاعلات التي حدثت بواسطة الغلوبلين المناعي E في اختبارات الوخز الجلدي التي أجريت على مرضى الأرجية ما مجموعه ٢١,٦٪ تفاعلاً إيجابياً تظهر انتباراً وحمامى خفيفة ومتوسطة وقوية.

الاستنتاج: تظهر النتائج أن أبواغ "ألترناريا" منتشرة كمكون رئيسي في بيئة الهواء الطلق في المملكة وتبلغ معظم ذرواتها في شهري أبريل وأكتوبر. يشير إجمالي ٢١,٦٪ من التفاعلات الإيجابية لاختبارات الوخز الجلدي إلى مستوى التحسيس أو إلى الحساسية متصالبة التفاعل لمستأرجات "الترناريا". توحي هذه الدراسة بأن "ألترناريا" المحمولة بالهواء قد تكون محسساً أرجياً محتملاً لدى الأشخاص المستعدين وقد تكون عاملاً مساعداً على الإصابة لدى الأشخاص المحسسين الذين يعانون من أعراض الربو القصبي والتهاب الأنف الأرجي في المملكة العربية السعودية.
المدونات الطبية السعودية ١٩٩٨، ١٨ (٦): ٤٩٧-٥٠١.

عسر الهضم والخمج باللولبية البوابية دراسة تحليلية لمئتي حالة أحيلوا للتنظير الداخلي في الكويت

مقدمة: يعتبر عسر الهضم من الأعراض الشائعة جداً، ويشكل السبب الأول لمعظم الحالات التي تحال لإجراء تنظير داخلي للعفج والمعدة والمريء. في حين أن القرحة الهضمية، والجزر المعدي المريئي، وسرطان المعدة لا تُمثل سوى أقلية من المرضى. بيدّ أن غالبية المرضى لم تبد شذوذات هامة (عسر هضم غير تقرحي). شكل الخمج بالعصيات اللولبية البوابية جزءاً من الأسباب المرضية للقرحة الهضمية مؤخراً. ونظراً لإمكانية تشخيص هذه العصيات بالوسائل غير الباضعة، فقد استقر الرأي على ضرورة قصر إجراء التنظير الداخلي على المرضى الإيجابيين الذين لا يستجيبون للمعالجة المضادة للجراثيم.

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المجلد ١٨ العدد ٦ رجب ١٤١٩ هـ نوفمبر ١٩٩٨م

المدونـــات الطبيـة السعوديـة

رئيس التحرير: الدكتور محمد أختر

هيئـة التحريـر

الدكتور مبارك الفاران
الدكتور عبدالعزيز المشاري
الدكتور عدنان عزت
الدكتور محمد زهير القاوي
الدكتور حُسن فريحة
الدكتور ربريت استورت
الدكتور منصور النزهة
الدكتور ثروة حسين
الدكتور فرنسيس ليلونك
الدكتور سلطان السديري
الدكتور محمد المقرن

هيئـة النشـر:

رئيس التحرير: الدكتور محمد أختر
المحرر الإداري: الدكتور سعدي طاهر
محرر النصوص العربية: الدكتور محمد زهير القاوي
محرر فني: رينه دايمكمان
محرر الإحصائيات: بشير خـــان

مساعدتا التحرير:

ماريان ريجينا ليوغ
ما. فليبيناس البانه ـ كاستيلانو

المدونات الطبية السعودية مجلة تنشر بموجب الأمر الملكي السامي رقم ٥/م/٢٤٢٢٣ بتاريخ ١٤ شوال عام ١٤٠٠هـ. وتصدر مرة كل شهرين، وهي مشروع مشترك بين كل من كلية الطب ومستشفى الملك خالد الجامعي ـ جامعة الملك سعود، صندوق بريد ٢٩٢٥ ـ الرياض ١١٤٦١، المملكة العربية السعودية، ومستشفى الملك فيصل التخصصي ومركز الأبحاث، صندوق بريد ٣٣٥٤ ـ الرياض ١١٢١١، المملكة العربية السعودية. يتم صف وطبع المجلة بمطابع جامعة الملك سعود. يتم توزيع المدوَّنات بواسطة قسم البريد التابع لإدارة الخدمات الإدارية بمستشفى الملك فيصل التخصصي ومركز الأبحاث. كما يتولى قسم الترجمة في هذه الإدارة إعداد الملخصات العربية بالاشتراك مع الدكتور محمد زهير القاوي. كل المراسلات والاستفسارات وطرق الحصول على المستلات ترسل إلى مكتب المطبوعات على العنوان التالي:

مكتب المطبوعات
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الرياض (١١٢١١) ـ المملكة العربية السعودية
ت: (٧٢٧٢-٤٦٤-٠١) تحويلة (١٨١٩/١٨١٥)
فاكس: (٧٢٣٧-٤٤٢-٠١-٩٦٦)

المسئول عن الإعلان:
مؤسسة فايد للإعلان ـ آي، بي، آي، إس.
الرياض ـ المملكة العربية السعودية
ت: (٣٧/٠٦٣٥-٤٧٧-٠١)
فاكس: (٣١٦٧-٤٧٨-٠١)
ممثل آي، بي، آي، إس في أوروبا وشمال أميركا:
مؤسسة سي، بي، إي.
المكتب الرئيسي في أوروبا ـ لندن
ت: (١٧٧٣-٩٨٧-٧١-٤٤) فاكس: (٩٠٢٢-٥٣٧٠-١٧١-٤٤)
المكتب الرئيسي في شمال أميركا ـ ميامي
ت: (٣٧٤١-٥٤٦-٢٠٧-١)
فاكس: (٣٣٥٠-٥٤٦-٢٠٧-١)

الآراء التي ترد في المقالات المنشورة تعبر عن رأي أصحابها فقط ولا تعبر عن وجهة نظر مجلة المدونات الطبية السعودية. لا يسمح بإعادة طبع أي جزء من المجلة أو نسخة بأي شكل وبأي وسيلة سواء أكانت إليكترونية أو آلية، بما في ذلك التصوير والتسجيل أو الإدخال في أي نظام حفظ أو استعادة معلومات إليكتروني، بدون الحصول على موافقة مسبقة من إدارة المجلة.